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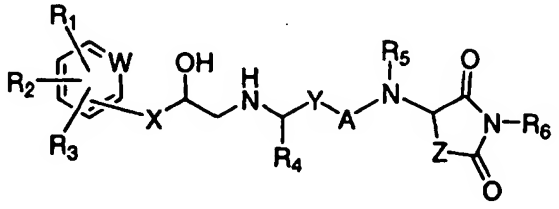

(I)

(57) Abstract: This invention provides compounds of Formula I the structure (A) wherein, A, X, Y, Z, W, R_1, R^2, R_3, R_4, R_5, and R_6 are as defined hereinbefore or a pharmaceutically acceptable salt thereof, which are useful in treating or inhibiting metabolic disorders related to insulin resistance or hyperglycemia (typically associated with obesity or glucose intolerance), atherosclerosis, gastrointestinal disorders, neurogenetic inflammation, glaucoma, ocular hypertension and frequent urination; and are particularly useful in the treatment or inhibition of type II diabetes.

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AZOLIDINES AS BETA-3 ADRENERGIC RECEPTOR AGONISTS

This invention relates to azolidine derivatives which are β_3 adrenergic receptor agonists useful for the treatment of metabolic disorders related to insulin resistance or hyperglycemia (typically associated with obesity or glucose intolerance), atherosclerosis, gastrointestinal disorders, neurogenetic inflammation, glaucoma, ocular hypertension, and frequent urination; and are particularly useful in the treatment of type II diabetes.

The subdivision of β adrenergic receptors (β-AR) into β_1- and β_2-AR has led to the development of β_1- and β_2- antagonists and/or agonists which have been useful for the treatment of cardiovascular disease and asthma. The recent discovery of "atypical" receptors, later called β_3-AR, has led to the development of β_3-AR agonists which may be potentially useful as antiobesity and antidiabetic agents. For recent reviews on β_3-AR agnoists , see: 1. A. D. Strosberg, Annu. Rev. Pharmacol. Toxicol. 1997, *37*, 421; 2. A. E. Weber, Ann. Rep. Med. Chem. 1998, *33*, 193; 3. C. P. Kordik and A. B. Reitz, J. Med. Chem. 1999, *42*, 181; 4. C. Weyer, J. F. Gautier and E. Danforth, Diabetes and Metabolism, 1999, *25*, 11.

Compounds that are potent and selective β_3 agonists, may be potentially useful antiobesity agents. Low levels or lack of β_1 and β_2-agonistic properties will minimize or eliminate the adverse side effects that are associated with β_1 and β_2 agonistic activities, i.e. increased heart rate, and muscle tremor, respectively.

Early developments in the β_3-agonist field are described in European patent 427480, US patents 4396627, 4478849, 4999377, 5153210. Although the early developments purport to claim compounds with greater β_3-AR selectivity over the β_1- and β_2-AR. However, clinical trials in humans with those early developed β_3-agonists have, so far, not been successful.

More recently, potent and selective human β_3 agonists have been described in several patents and published applications: WO 98/32753, WO 97/46556, WO 97/37646,

WO 97/15549, WO 97/25311, WO 96/16938, WO 95/29159, European Patents 659737, 801060, 714883, 764640, 827746, and US Patents 5561142, 5705515, 5436257, and 5578620. These compounds were evaluated in Chinese hamster ovary (CHO) cells test procedures, expressing cloned human β3 receptors, which predict the effects that can be expected in humans (Granneman et al., *Mol Pharmacol.*, **1992**, *42*, 964; Emorine et al., *Science*, **1989**, *245*, 1118; Liggett *Mol. Pharmacol.*, **1992**, *42*, 634).

β_3-Adrenergic agonists also are useful in controlling the frequent urge of urination. It has been known that relaxation of the bladder detrusor is under beta adrenergic control (Li JH, Yasay GD and Kau ST *Pharmacology* 1992; **44**: 13-18). Beta-adrenoceptor subtypes are in the detrusor of guinea-pig urinary bladder. Recently, a number of laboratories have provided experimental evidence of β_3 adrenergic receptors in a number of animal species including human (Yamazaki Y, Takeda H, Akahane M, Igawa Y, et al. *Br. J. Pharmacol.* 1998; **124**: 593-599), and that activation of the β_3 receptor subtype by norepinephrine is responsible for relaxation of the urinary bladder.

Urge urinary incontinence is characterized by abnormal spontaneous bladder contractions that can be unrelated to bladder urine volume. Urge urinary incontinence is often referred to hyperactive or unstable bladder. Several etiologies exist and fall into two major categories, myogenic and neurogenic. The myogenic bladder is usually associated with detrusor hypertrophy secondary to bladder outlet obstruction, or with chronic urinary tract infection. Neurogenic bladders are associated with an uninhibited micturition reflex. An upper motor neuron disease is usually the underlying cause. In either case, the disease is characterized my abnormal spontaneous contractions that result in an abnormal sense of urinary urgency and involuntary urine loss. At present, the most common therapy for hyperactive bladder includes the use of antimuscarinic agents to block the action of the excitatory neurotransmitter acetylcholine. While effective in neurogenic bladders, their utility in myogenic bladders is questionable. In addition, due to severe dry mouth side-effects associated with antimuscarinic therapy, the patient compliance with these agents is only approximately 30%.

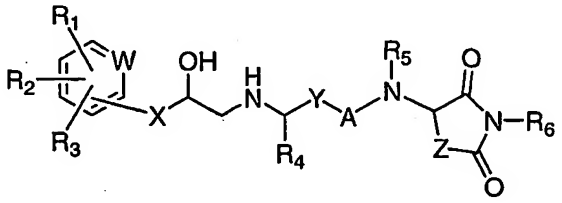
In the bladder, β_3 adrenergic receptor agonists activate adenylyl cyclase and generate cAMP through the G-protein coupled β_3 receptor. The resulting phosphorylation of phospholamban/calcium ATPase enhances uptake of calcium into the sarcoplasmic reticulum. The decrease in intracellular calcium inhibits bladder smooth muscle contractility.

It is suggested therefore, that activation of the β_3 adrenergic receptor in the urinary bladder will inhibit abnormal spontaneous bladder contractions and be useful for the treatment of bladder hyperactivity. Note, that unlike the antimuscarinics, β_3 adrenergic receptor agonists would be expected to be active against both neurogenic and myogenic etiologies.

Despite all these recent developments there is still no single therapy available for the treatment of type II diabetes (NIDDM), obesity, atherosclerosis, gastrointestinal disorders, neurogenetic inflammation, frequent urination and related diseases. A potent and selective β_3 adrenergic receptor agonist is therefore highly desirable for the potential treatment of such disease states.

DESCRIPTION OF THE INVENTION

This invention provides compounds of Formula I having the structure



I

wherein,

R_1, R_2, R_3 are each, independently, hydrogen, alkyl of 1-6 carbon atoms, aryl of 6 to 10 carbon atoms, aryloxy of 6-10 carbon atoms, halogen, trifluoromethyl of 1-6 carbon atoms, arylalkoxy of 7-14 carbon atoms, arylalkyl of 7-14 carbon atoms, alkoxy of 1-6 carbon atoms, hydroxy, nitro, amino, aminocarbonyl, alkylamino of 1-6 carbon atoms, dialkyl amino of 1-6 carbon atoms per alkyl group, formamido, ureido, acyl of 2-7 carbon atoms, acylamino of 2-7 carbon atoms, amino,

alkylsulfonylamino of 1-6 carbon atoms, or arylsulfonylamino of 6 to 10 carbon atoms; or two of R_1, R_2, and R_3 are taken together to form a phenyl ring or a heterocyclic ring which is fused to the ring which contains the R_1, R_2, or R_3 substituents, wherein the heterocyclic ring contains 1-3 heteroatoms selected from N, O, or S;

R_4 is hydrogen or alkyl of 1-6 carbon atoms;

R_5 is hydrogen, alkyl of 1-6 carbon atoms, aryl of 6-10 carbon atoms, arylalkyl of 7-14 carbon atoms, halogen substituted arylalkyl of 7-14 carbon atoms, arylalkene of 8-16 carbon atoms, arylalkyne of 8-16 carbon atoms, alkoxycarbonyl of 2-7 carbon atoms, aryloxycarbonyl of 7-11 carbon atoms, alkylsulfonyl of 1-6 carbon atoms, arylsulfonyl of 1-6 carbon atoms, halogen substituted arylalkene of 8-16 carbon atoms, or halogen substituted arylalkyne of 8-16 carbon atoms;

R_6 is hydrogen, alkyl of 1-6 carbon atoms, aryl or arylalkyl of 7-14 carbon atoms;

A is phenyl, naphthyl, benzofuryl, or benzothienyl;

X is bond, $-OCH_2-$, or $-SCH_2-$;

Y is alkyl of 1-6 carbon atoms, or alkoxy of 1-6 carbon atoms or a bond;

Z is carbon, sulfur, oxygen, or nitrogen;

W is carbon or nitrogen;

or a pharmaceutically acceptable salt thereof, which are selective agonists at human β_3 adrenergic receptors and are useful in treating or inhibiting metabolic disorders related to insulin resistance or hyperglycemia (typically associated with obesity or glucose intolerance), atherosclerosis, gastrointestinal disorders, neurogenetic inflammation, glaucoma, ocular hypertension, and frequent urination; and are particularly useful in the treatment or inhibition of type II diabetes.

Pharmaceutically acceptable salts can be formed from organic and inorganic acids, for example, acetic, propionic, lactic, citric, tartaric, succinic, fumaric, maleic, malonic, mandelic, malic, phthalic, hydrochloric, hydrobromic, phosphoric, nitric, sulfuric, methanesulfonic, naphthalenesulfonic, benzenesulfonic, toluenesulfonic, camphorsulfonic, and similarly known acceptable aids when a compound of this invention contains a basic moiety. Salts may also be formed from organic and inorganic bases, such as alkali metal salts (for example, sodium, lithium, or potassium) alkaline earth metal salts, ammonium

salts, alkylammonium salts containing 1-6 carbon atoms or dialkylammonium salts containing 1-6 carbon atoms in each alkyl group, and trialkylammonium salts containing 1-6 carbon atoms in each alkyl group, when a compound of this invention contains an acidic moiety.

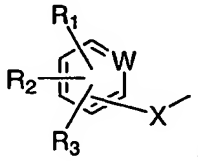
Alkyl as a group or part of a group includes both straight chain as well as branched moieties eg of 1-4 carbon atoms such as methyl, ethyl, propyl, isopropyl and butyl. Alkenyl and alkynyl as a group or part of a group include both straight chain as well as branched moieties, eg having 2-6 carbon atoms, which contain at least one alkene or alkyne group. By definition alkyl also includes alkyl moieties which are optionally mono- or poly substituted with groups such as halogen, hydroxy, cyano, alkoxy, aryloxy, arylalkyl, alkylthio, arylthio, amino, alkylamino, and dialkylamino. Halogen means bromine, chlorine, fluorine, and iodine. The term "aryl" as a group or part of a group means a carbocyclic aromatic ring system of 6-10 carbon atoms such as phenyl and naphthyl.

As used herein, a heterocyclic ring is a ring containing 1-3 heteroatoms selected from N, O and S, which may be saturated, unsaturated, or partially unsaturated eg of 5-10 ring members. As described herein, the term heterocycle includes heterocyclic rings or ring systems in which carbon atoms may exist as a carbonyl group or as an oxime of a carbonyl group. It is understood that the heterocyclic ring does not contain heteroatoms in arrangements which would make them inherently unstable. For example, the term heterocyclic ring does not include ring systems containing O-O bonds in the ring backbone. Examples of heterocycles include 5-10 membered rings, eg pyrrolyl, pyrrolidinyl, imidazolyl, indolinyl, thienyl, furyl, 1,3-dioxolane and imidazolidin-2-one. When any two of R_1, R_2, or R_3 are taken together to form a heterocyclic ring, the resulting heterocycles are fused to a phenyl ring or a pyridyl ring. Either ring of the fused heterocycle may contain the R_1, R_2 or R_3 substitutent which is not part of the ring backbone. Similarly when any two of R_1, R_2, or R_3 are taken together to form a phenyl ring, the resulting fused moiety will be a naphthyl, quinolinyl or an isoquinolinyl ring. Either ring of the fused moiety may contain the R_1, R_2 or R_3 substitutent which is not part of the ring backbone. When two of R_1, R_2 or R_3 are taken together to form a heterocyclic ring, preferred phenyl fused heterocyclic rings include 1,3-dihydro-

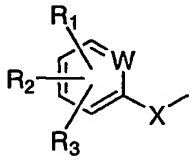
benzimidazolone, carbazole, benzofuran and 1,3-benzodioxole. When two of R_1, R_2 or R_3 are taken together to form a phenyl ring, preferred fused rings include naphthyl.

The compounds of the present invention contain at least one asymmetric center. Additional asymmetric centers may exist on the molecule depending upon the structure of the substituents on the molecule. The compounds may be prepared as a racemic mixture and can be used as such, or may be resolved into the individual isomers. In addition to covering the racemic compounds, this invention also covers all individual isomers, enantiomers, diasteromers or mixtures thereof, regardless of whether the structural representations of the compounds indicate such stereochemistry.

Examples of



are



where W is N or C, eg 2-pyridyl.

X may be for example $-OCH_2$ or a bond.

A may be for example phenyl.

W may be carbon or nitrogen.

R_4 may be hydrogen or alkyl of 1-6 carbon atoms.

R_5 may be hydrogen or alkyl of 1-6 carbon atoms.

R_6 may be hydrogen or alkyl of 1-6 carbon atoms.

Preferred compounds of Formula I are those having one or more (e.g. all) the following values:

R_1, R_2, R_3 are each, independently, hydrogen, alkyl of 1-6 carbon atoms, aryl of 6 to 10 carbon atoms, aryloxy of 6-10 carbon atoms, halogen, arylalkoxy of 7-14 carbon atoms, arylalkyl of 7-14 carbon atoms, alkoxy of 1-6 carbon atoms, hydroxy, or alkylsulfonylamino of 1-6 carbon atoms; or two of R_1, R_2, and R_3 are taken together to form a heterocyclic ring which is fused to the ring which contains the R_1, R_2, or R_3 substituents, wherein the heterocyclic ring contains 1-3 heteroatoms selected from N, O, or S;

R_4 is hydrogen or alkyl of 1-6 carbon atoms;

R_5 is hydrogen, alkyl of 1-6 carbon atoms, halogen substituted arylalkyl of 7-14 carbon atoms, or halogen substitued arylalkyne of 8-16 carbon atoms;

R_6 is hydrogen, or alkyl of 1-6 carbon atoms;

A is phenyl, or benzofuryl;

X is bond, or $-OCH_2-$;

Y is alkyl of 1-6 carbon atoms or a bond;

Z is sulfur;

W is carbon or nitrogen;

or a pharmaceutically acceptable salt thereof.

Specifically preferred compounds of this invention are:

a) 5-[4-(2-{[(2*S*)-2-Hydroxy-3-(4-phenoxyphenoxy)propyl]amino}ethyl)anilino]-1,3-thiazolidine-2,4-dione;

b) 5-{4-[2-({(2*S*)-3-[4-(Benzyloxy)phenoxy]-2-hydroxypropyl}amino)ethyl]anilino}-3-methyl-1,3-thiazolidine-2,4-dione;

c) 5-[4-(2-{[(2*R*)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino}ethyl)anilino]-3-methyl-1,3-thiazolidine-2,4-dione;

d) 5-{4-[2-({(2*S*)-3-[4-(Benzyloxy)phenoxy]-2-hydroxypropyl}amino)ethyl]anilino}-1,3-thiazolidine-2,4-dione;

e) 5-[4-(2-{[(2*S*)-2-Hydroxy-3-(4-hydroxyphenoxy)propyl]amino}ethyl)anilino]-1,3-thiazolidine-2,4-dione;

f) 5-[4-(2-{[(2*R*)-2-(3-Chlorophenyl)-2-hydroxy-ethyl]amino}ethyl)anilino]-1,3-thiazolidine-2,4-dione;

g) 5-[4-(2-{[(2*R*)-2-Hydroxy-2-phenylethyl]amino}ethyl)anilino]-1,3-thiazolidine-2,4-dione;

h) 5-[4-(2-{[(2*S*)-3-(4-Fluorophenoxy)-2-hydroxypropyl]amino}ethyl)anilino]-1,3-thiazolidine-2,4-dione;

i) 5-[4-(2-{[(2*S*)-2-Hydroxy-3-phenoxypropyl]amino}ethyl)anilino]-1,3-thiazolidine-2,4-dione;

j) 5-[4-(2-{[(2*S*)-2-Hydroxy-3-(4-methoxyphenoxy)propyl]amino}ethyl)anilino]-1,3-thiazolidine-2,4-dione;

k) 5-{4-[2-({(2*S*)-3-[3-(Benzyloxy)phenoxy]-2-hydroxypropyl}amino)ethyl]anilino}-1,3-thiazolidine-2,4-dione;

l) 5-[4-(2-{[(2*S*)-2-Hydroxy-3-(3-hydroxyphenoxy)propyl]amino}ethyl)anilino]-1,3-thiazolidine-2,4-dione;

m) 5-[4-(2-{[(2*S*)-3-(9*H*-Carbazol-4-yloxy)-2-hydroxypropyl]amino}ethyl)anilino]-1,3-thiazolidine-2,4-dione;

n) *N*-{5-[(1*S*)-2-({4-[(2,4-Dioxo-1,3-thiazolidin-5-yl)amino]phenethyl}amino)-1-hydroxyethyl]-2-hydroxyphenyl}methanesulfonamide;

o) 5-[4-(2-{[(2*S*)-3-(1-Benzofuran-5-yloxy)-2-hydroxypropyl]amino}ethyl)anilino]-1,3-thiazolidine-2,4-dione;

p) 5-[4-(2-{[(2*S*)-3-(4-Butoxyphenoxy)-2-hydroxypropyl]amino}ethyl)anilino]-1,3-thiazolidine-2,4-dione;

q) 5-[4-(2-{[(2*S*)-2-Hydroxy-3-phenoxypropyl]amino}ethyl)(methyl)anilino]-1,3-thiazolidine-2,4-dione.;

r) 5-[4-(2-{[(2*R*)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino}propyl)anilino]-1,3-thiazolidine-2,4-dione;

s) 5-{4-[2-({(2*R*)-2-Hydroxy-3-[(2-oxo-2,3-dihydro-1*H*-benzimidazol-4-yl)oxy]propyl}-amino)ethyl]anilino}-1,3-thiazolidine-2,4-dione;

t) 5-{[2-({[(2*R*)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino}methyl)-1-benzofuran-5-yl]-amino}-1,3-thiazolidine-2,4-dione;

u) 5-(4-{2-[(2S)-2-Hydroxy-3-(naphthalen-2-yloxy)-propylamino]-ethyl}-phenylamino)-thiazolidine-2,4-dione;

v) 5-(4-{2-[(2S)-3-(Biphenyl-4-yloxy)-2-hydroxy-propylamino]-ethyl}- phenylamino)-thiazolidine-2,4-dione;

w) 5-(4-{2-[2-Hydroxy-3-(naphthalen-1-yloxy)-propylamino]-ethyl}- phenylamino)-thiazolidine-2,4-dione;

x) 5-(4-{2-[(2S)-3-(Benzo[1,3]dioxol-5-yloxy)-2-hydroxy-propylamino]ethyl}-phenyl-amino)-thiazolidine-2,4-dione;

y) 5-(4-{2-[(2S)-3-(4-Benzyloxy-phenoxy)-2-hydroxy-propylamino]-ethyl}-phenylamino)-thiazolidine-2,4-dione;

z) 5-[(4-{2-[(2S)-3-(4-Benzyloxy-phenoxy)-2-hydroxy-propylamino]-ethyl}- phenyl)-(4-bromo-benzyl)-amino]-thiazolidine-2,4-dione;

aa) 5-[(4-{2-[(2S)-3-(4-Benzyloxy-phenoxy)-2-hydroxy-propylamino]-ethyl}-phenyl)-methyl-amino]-thiazolidine-2,4-dione;

bb) 5-[(4-{2-[(2S)-3-(4-Benzyloxy-phenoxy)-2-hydroxy-propylamino]-ethyl}- phenyl)-[3-(4-fluoro-phenyl)-prop-2-ynyl]-amino}-thiazolidine-2,4-dione;

cc) 5-[(4-Bromo-benzyl)-(4-{2-[(2S)-2-hydroxy-3-(4-hydroxy-phenoxy)-propylamino]-ethyl}-phenyl)-amino]-thiazolidine-2,4-dione;

dd) 5-((4-Bromo-benzyl)-{4-[2-((2S)-2-hydroxy-3-phenoxy-propylamino)ethyl]-phenyl}-amino)-thiazolidine-2,4-dione;

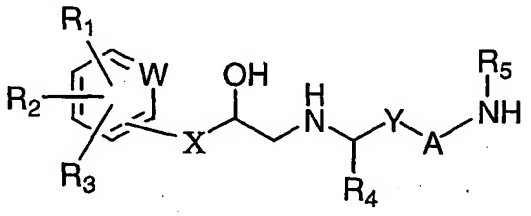
ee) 5-{4-[2-((2S)-2-Hydroxy-2-pyridin-3-yl-ethylamino)ethyl]phenylamino}thiazolidine-2,4-dione; and

ff) 5-{4-[2-((2R)-2-Hydroxy-2-pyridin-3-yl-ethylamino)ethyl]phenylamino}thiazolidine-2,4-dione

or a pharmaceutically acceptable salt thereof.

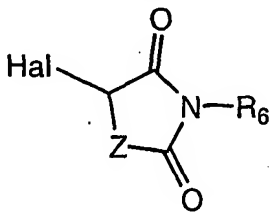
This invention also provides processes for preparing compounds of formula I which processes comprise one of the following:

a) reacting a compound of formula II



II

wherein R_1, R_2, R_3, R_4, R_5, W, X, Y and A are as defined herein, where necessary any reactive substituent group being protected; with a compound of formula III



III

wherein Z and R_6 are as defined defined herein, and Hal is halogen, where necessary any reactive substituent group being protected;

to give a compound of formula I as defined herein;

or

b) removing any protecting groups from a compound of formula I in which at least one substituent carries a protecting group to give a compound of formula I;

or

c) converting a basic compound of formula I to a salt thereof by reaction with a pharmaceutically acceptable acid;

or

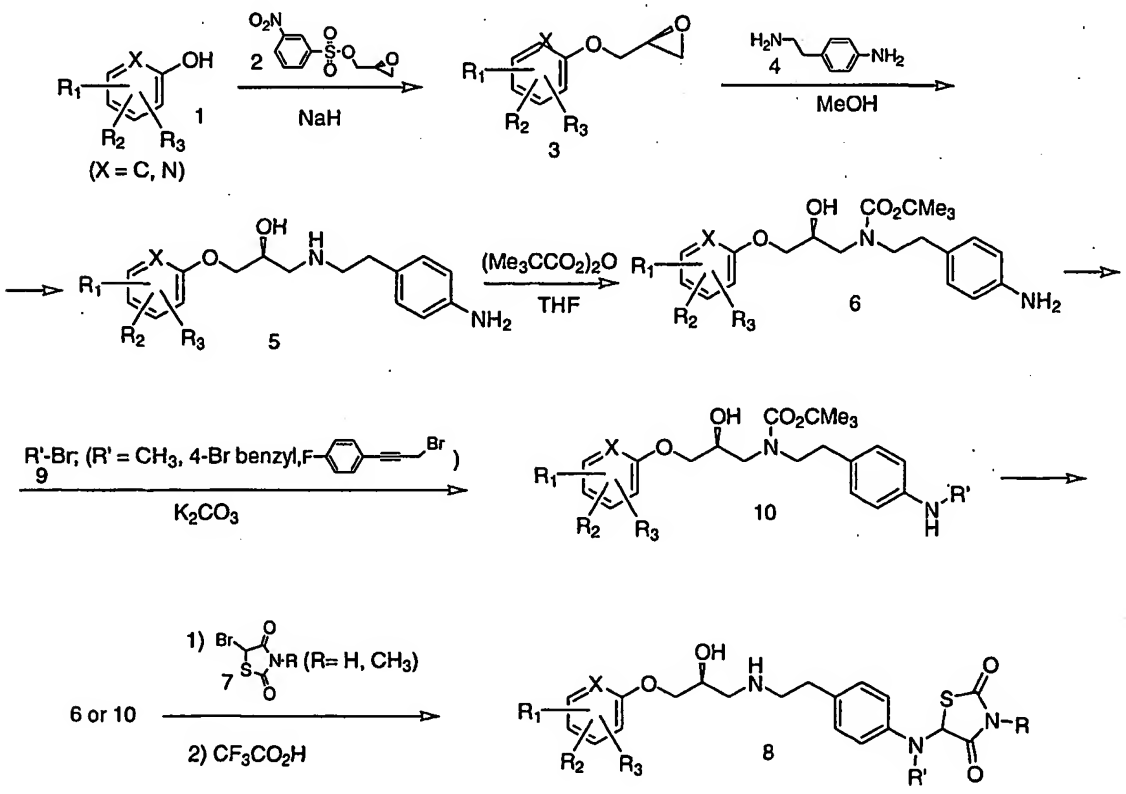
d) converting a compound of formula I having one or more reactive substituent groups to a different compound of formula I;

or

e) isolating an isomer of a compound of formula I from a mixture thereof.

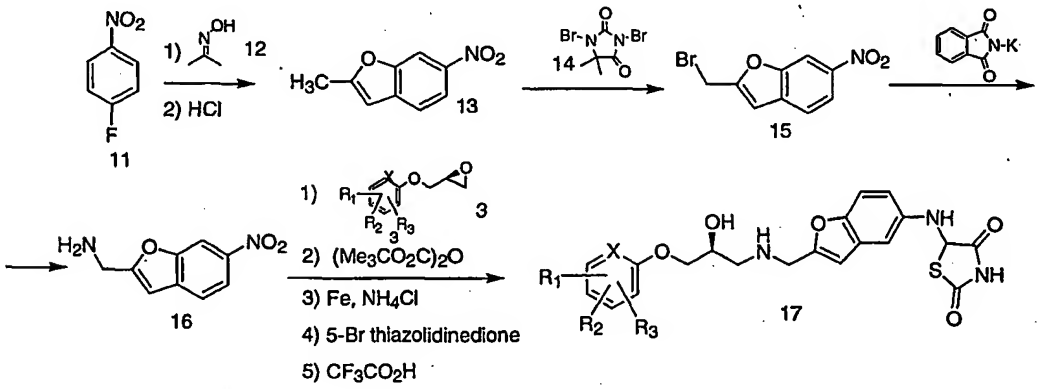
The compounds of this invention may be prepared for example according to the following schemes from commercially available starting materials or starting materials which can be prepared using literature procedures. These schemes show the preparation of representative compounds of this invention.

Scheme I



In Scheme I, hydroxyl compounds of structure 1 which are either commercially available or can be prepared by known methods (ref. EP 0764640), can be alkylated with glycidyl benzenesulfonates 2 in the presence of a base, i.e. sodium hydride to produce epoxides 3. Styrene oxides that were used in this invention were commercially available. Refluxing either epoxides 3 or styrene oxides with aniline 4 produced compounds 5. The amino group can be protected selectively using di-tert-butyl dicarbonate at low temperatures (0 ^{0}C) to produce carbamates 6. Treatment of the carbamates 6 with bromo-thiazolidinediones 7 in the presence of a base, i.e. triethylamine, in polar solvents, i.e. N,N-dimethylformamide, followed by acidic hydrolysis with either organic or inorganic acids, i.e. trifluoroacetic acid, produced thiazolidinediones 8. The required bromo-thiazolidinediones 7 were prepared according to known methods (ref. *J. Med. Chem.*, **1990**, *33* 1418-1423). Alkylation of 6 with various alkylating agents 9 in the presence of a base, i.e. potassium carbonate, produced anilines 10. Substituted anilines 10 react with the bromo-thiazolidinediones 7, similarly to anilines 6, to produce alkylated analogues 8.

Scheme II



In Scheme II, nitrobenzene 11 was treated with acetoxime in the presence of a base, i.e. sodium hydride, followed by treatment with an ethanolic solution of hydrochloric acid to produce benzofuran 13. Bromination of 13 with 1,3-dibromo-5,5-dimethyl-hydantoin under UV light gave bromide 15. Conversion of 13 to amine 16 was accomplished in two steps, first alkylation with potassium phthalimide in acetonitrile in the presence crown ether (18-C-6), followed by hydrolysis with hydrazine/ethanol. Amine 16 was converted to the thiazolidinedione 17, in substantially the same manner as in Scheme I.

The compounds of this invention are useful in treating metabolic disorders related to insulin resistance or hyperglycemia, typically associated with obesity or glucose intolerance. The compounds of this invention are therefore, particularly useful in the treatment or inhibition of type II diabetes. The compounds of this invention are also useful in modulating glucose levels in disorders such as type I diabetes.

The ability of compounds of this invention to treat or inhibit disorders related to insulin resistance or hyperglycemia was established with representative compounds of this invention in the following standard pharmacological test procedures, which measured the binding selectivity to the β_1, β_2, and β_3 adrenergic receptors. Binding to the receptors was measured in Chinese Hamster ovary (CHO) cells that were transfected with adrenergic receptors. The following briefly summarizes the procedures used and results obtained.

Transfection of CHO cells with β_1 and β_2 adrenergic receptors: CHO cells were transfected with human β_1- or β_2-adrenergic receptors as described in *Tate, K.M., , Eur. J. Biochem., 196:357-361 (1991).*

Cloning of Human β_3-AR Genomic DNA: cDNA was constructed by ligating four polymerase chain reaction (PCR) products using the following primers: an ATG-NarI fragment, sense primer 5'-CTTCCCTACCGCCCCACGCGCGATC3' and anti-sense primer 5'CTGGCGCCCAACGGCCAGTGGCCAGTC3'; a NarI-AccI fragment, 5'TTGGCGCTGATGGCCACTGGCCGTTTG3' as sense and 5'GCGCGTAGACGAAGAGCATCACGAG3' as anti-sense primer; an AccIi-StyI fragment, sense primer 5'CTCGTGATGCTCTTCGTCTCACGCGC3' and anti-sense primer 5'GTGAAGGTGCCCATGATGAGACCCAAGG3' and a StyI-TAG fragment, with sense primer 5'CCCTGTGCACCTTGGGTCTCATCATGG3' and anti-sense primer 5'CCTCTGCCCCGGTTACCTACCC3'. The corresponding primer sequences are described in *Mantzoros, C.S., et.al., Diabetes 45: 909-914 (1996).* The four fragments are ligated into a pUC 18 plasmid (Gibco-BRL) and sequenced. Full length β_3 AR clones (402 amino acids) containing the last 6 amino acids of hβ_3_AR are prepared with the β_3-β ARpcDNA3 from ATTC.

Binding Procedure: Clones expressing receptor levels of 70 to 110 fmoles/mg protein were used in the test procedures. CHO cells were grown in 24-well tissue culture plates in Dulbecco's Modified Eagle Media with 10% fetal bovine serum, MEM non-essential amino acids, Penicillin-Streptompycin and Geneticin. On the day of test procedure, growth medium was replaced with preincubation media (Dulbecco's Modified Eagle Media and incubated for 30 minutes at 37° C. Preincubation medium was replaced with 0.2 ml treatment medium containing DMEM media containing 250 μM IBMX (isobutyl-1-methylxantine) plus 1 mM ascorbic acid with test compound dissolved in DMSO. Test compounds were tested over a concentration range of 10^{-9} M to 10^{-5} M for β_3 cells and 10^{-8} to 10^{-4} M for β_1 and β_2 transfected cells. Isoproterenol (10^{-5} M) was used as an internal standard for comparison of activity. Cells were incubated at 37° C. on a rocker for 30 min with the β_3 cells and 15 min for β_1 and β_2 cells. Incubation was stopped with the addition of 0.2N HCl and neutralized with 2.5N NaOH. The plates, containing the cells and neutralized media, were stored at -20 degrees celsius until ready to test for cAMP using the SPA test kit (Amersham).

Data Analysis and Results: Data collected from the SPA test procedure were analyzed as per cent of the maximal isoproterenol response at 10^{-5} M. Activity curves were plotted using the SAS statistical and graphics software. EC_{50} values were generated for each compound and the maximal response (IA) developed for each compound is compared to the maximal response of isoproternol at 10^{-5} M from the following formula:

$$IA = \frac{\text{\% activity compound}}{\text{\% activity isoproterenol}}$$

Table I shows the β3-adronergic receptor EC_{50} and IA values for the representative compounds of this invention that were evaluated in this standard pharmacological test procedure. These results show that compounds of the present invention have activity at the β3-adrenergic receptor. The compounds of this inventon had weaker or no activity at β1 and/or β2-adrenergic receptor.

Table I

Compound No.	E $C_{50}(\beta 3, nM)$	IA(β3)
Example 4	1	85
Example 5	20	99
Example 6	7	83
Example 7	83	94
Example 8	14	66
Example 9	0.9	98
Example 12	3	117
Example 13	12	104
Example 14	9	111
Example 17	17	68
Example 18	9	89
Example 19	20	71
Example 29	3	109
Example 31	96	88

Based on the results obtained in these standard pharmacological test procedures, representative compounds of this invention have been shown to be selective β_3 adrenergic receptor agonists and are therefore useful in treating metabolic disorders related to insulin resistance or hyperglycemia (typically associated with obesity or glucose intolerance), atherosclerosis, gastrointestinal disorders, neurogenetic inflammation, glaucoma, ocular hypertension, and frequent urination; and are particularly useful in the treatment or inhibition of type II diabetes, and in modulating glucose levels in disorders such as type I diabetes. As used herein, the term modulating means maintaining glucose levels within clinically normal ranges.

As used in accordance with this invention, the term providing an effective amount means either directly administering such a compound of this invention, or administering a prodrug, derivative, or analog which will form an effective amount of the compound of this invention within the body.

It is understood that the effective dosage of the active compounds of this invention may vary depending upon the particular compound utilized, the mode of administration, the condition, and severity thereof, of the condition being treated, as well as the various physical factors related to the individual being treated. As used in accordance with invention, satisfactory results may be obtained when the compounds of this invention are administered to the individual in need at a daily dosage of from about 0.1 mg to about 1 mg per kilogram of body weight, preferably administered in divided doses two to six times per day, or in a sustained release form. For most large mammals, the total daily dosage is from about 3.5 mg to about 140 mg. It is preferred that the administration of one or more of the compounds herein begin at a low dose and be increased until the desired effects are achieved.

Such doses may be administered in any manner useful in directing the active compounds herein to the recipient's bloodstream, including orally, via implants, parenterally (including intravenous, intraperitoneal and subcutaneous injections), rectally, intranasally, vaginally, and transdermally. For the purposes of this disclosure, transdermal administrations are understood to include all administrations across the surface of the body and the inner linings of bodily passages including epithelial and mucosal tissues. Such administrations may be carried out using the present compounds, or pharmaceutically acceptable salts thereof, in lotions, creams, foams, patches, suspensions, solutions, and suppositories (rectal and vaginal).

Oral formulations containing the active compounds of this invention may comprise any conventionally used oral forms, including tablets, capsules, buccal forms, troches, lozenges and oral liquids, suspensions or solutions. Capsules may contain mixtures of the active compound(s) with inert fillers and/or diluents such as the pharmaceutically acceptable starches (e.g. corn, potato or tapioca starch), sugars, artificial sweetening agents, powdered celluloses, such as crystalline and microcrystalline celluloses, flours, gelatins, gums, etc. Useful tablet formulations may be made by conventional compression, wet granulation or dry granulation methods and utilize pharmaceutically acceptable diluents, binding agents, lubricants, disintegrants, suspending or stabilizing agents, including, but not limited to, magnesium stearate, stearic acid, talc, sodium lauryl

sulfate, microcrystalline cellulose, carboxymethylcellulose calcium, polyvinylpyrrolidone, gelatin, alginic acid, acacia gum, , xanthan gum, sodium citrate, complex silicates, calcium carbonate, glycine, dextrin, sucrose, sorbitol, dicalcium phosphate, calcium sulfate, lactose, kaolin, mannitol, sodium chloride, talc, dry starches and powdered sugar. Oral formulations herein may utilize standard delay or time release formulations to alter the absorption of the active compound(s).

In some cases it may be desirable to administer the compounds directly to the airways in the form of an aerosol.

The compounds of this invention may also be administered parenterally or intraperitoneally. Solutions or suspensions of these active compounds as a free base or pharmacologically acceptable salt can be prepared in water suitably mixed with a surfactant such as hydroxy-propylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols and mixtures thereof in oils. Under ordinary conditions of storage and use, these preparation contain a preservative to prevent the growth of microorganisms.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g., glycerol, propylene glycol and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oils.

Suppository formulations may be made from traditional materials, including cocoa butter, with or without the addition of waxes to alter the suppository's melting point, and glycerin. Water soluble suppository bases, such as polyethylene glycols of various molecular weights, may also be used.

The compounds of the present invention also possess utility for increasing lean meat deposition and/or improving lean meat to fat ratio in edible animals, i.e. ungulate animals and poultry.

Animal feed compositions effective for increasing lean meat deposition and for improving lean meat to fat ratio in poultry, swine, sheep, goats, and cattle are generally prepared by mixing the compounds of the present invention with a sufficient amount of animal feed to provide from about 1 to 1000 ppm of the compound in the feed. Animal feed supplements can be prepared by admixing about 75% to 95% by weight of a compound of the present invention with about 5% to about 25% by weight of a suitable carrier or diluent. Carriers suitable for use to make up the feed supplement compositions include the following: alfalfa meal, soybean meal, cottonseed oil meal, linseed oil meal, sodium chloride, cornmeal, cane molasses, urea, bone meal, corncob meal and the like. The carrier promotes a uniform distribution of the active ingredients in the finished feed into which the supplement is blended. It thus performs an important function by ensuring proper distribution of the active ingredient throughout the feed. The supplement is used as a top dressing for the feed, it likewise helps to ensure uniformity of distribution of the active material across the top of the dressed feed.

The preferred medicated swine, cattle, sheep and goat feed generally contain from 0.01 to 400 grams of active ingredient per ton of feed, the optimum amount for these animals usually being about 50 to 300 grams per ton of feed. The preferred poultry and domestic pet feed usually contain about 0.01 to 400 grams and preferably 10 to 400 grams of active ingredient per ton of feed.

For parenteral administration the compounds of the present invention may be prepared in the form of a paste or a pellet and administered as an implant, usually under the skin of the head or ear of the animal in which increase in lean meat deposition and improvement in lean mean to fat ratio is sought. In general, parenteral administration involves injection of a sufficient amount of the compounds of the present invention to provide the animal with 0.001 to 100 mg/kg/day of body weight of the active ingredient. The preferred dosage for swine, cattle, sheep and goats is in the range of from 0.001 to 50 mg/kg/day of body weight of active ingredient; whereas, the preferred dose level for

poultry and domestic pets is usually in the range of from 0.001 to 35 mg/kg/day of body weight.

Paste formulations can be prepared by dispersing the active compounds in a pharmaceutically acceptable oil such as peanut oil, sesame oil, corn oil or the like. Pellets containing an effective amount of the compounds of the present invention can be prepared by admixing the compounds of the present invention with a diluent such as carbowax, carnuba wax, and the like, and a lubricant, such as magnesium or calcium stearate, can be added to improve the pelleting process. It is, of course, recognized that more than one pellet may be administered to an animal to achieve the desired dose level which will provide the increase in lean meat deposition and improvement in lean meat to fat ratio desired. Moreover, it has been found that implants may also be made periodically during the animal treatment period in order to maintain the proper drug level in the animal's body. For the poultry and swine raisers, using the method of the present invention yields leaner animals.

Additionally, the compounds of this invention are useful in increasing the lean mass to fat ratio in domestic pets, for the pet owner or veterinarian who wishes to increase leanness and trim unwanted fat from pet animals, the present invention provides the means by which this can be accomplished.

The following procedures describe the preparation of representative examples of this invention.

Example 1

5-[4-(2-{[(2*S*)-2-Hydroxy-3-(4-phenoxyphenoxy)propyl]amino}ethyl)anilino]-1,3-thiazolidine-2,4-dione

Step a) (2*S*)-2-[(4-Phenoxyphenoxy)methyl]oxirane

Sodium hydride (60% in mineral oil, 1.08 g, 26.9 mmol) was added portionwise into a cold (0^0C) mixture of 4-phenoxyphenol (5.0 g, 26.9 mmol) and N,N-dimethylformamide (50 mL). The mixture was stirred for 1 hour and then (2*S*)-oxiranylmethyl 3-nitrobenzene-sulfonate (7.67 g, 29.6 mmol) in N,N-dimethylformamide (10 mL) was added dropwise. The new mixture was stirred at room temperature for 18 hours, poured into water and extracted with ethyl acetate. The organic extracts were dried over $MgSO_4$. Evaporation

and purification by flash chromatography (hexanes/ethyl acetate 5/1) gave a clear oil (6.2 g, 95% yield): MS *m/e* 242 M^+.

Step b) (2*S*)-1-[(4-Aminophenethyl)amino]-3-(4-phenoxyphenoxy)-2-propanol

A mixture of (2*S*)-2-[(4-phenoxyphenoxy)methyl]oxirane (6.0 g, 24.8 mmol), 4-(2-aminoethyl)aniline (10.1 g, 74.4 mmol), and methyl alcohol (100 mL) was refluxed for 5 hours. The volatiles were removed in vacuo and the residue was purified by flash chromatography (hexanes/ethyl acetate/methyl alcohol 1/1/1) to give a white solid (6.6 g, 70% yield): MS *m/e* 379 $(M+H)^+$;

Analysis for: $C_{23}H_{26}N_2O_3$ Calc'd: C, 72.99; H, 6.93; N, 7.40 Found: C, 72.41; H, 6.93; N, 7.33

Step c) *tert*-Butyl 4-aminophenethyl[(2*S*)-2-hydroxy-3-(4-phenoxyphenoxy)propyl]-carbamate

Di-*tert*-butyl dicarbonate (2.88 g, 13.2 mmol) was added into a cold (0 ^{0}C) mixture of (2*S*)-1-[(4-aminophenethyl)amino]-3-(4-phenoxyphenoxy)-2-propanol (5.0 g, 13.2 mmol), and tetrahydrofuran (20 mL). The mixture was stirred at 0 ^{0}C for 2 hours , poured into water, and extracted with ethyl acetate. The organic extracts were dried over $MgSO_4$. Evaporation and purification by flash chromatography (hexanes/ethyl acetate 1/1) gave a yellow oil (5.96 g, 95% yield): MS *m/e* 479 $(M+H)^+$;

Analysis for: $C_{28}H_{24}N_2O_5$ Calc'd: C, 70.27; H, 7.16; N, 5.85 Found: C, 70.14; H, 6.88; N, 5.73

Step d) *tert*-Butyl 4-[(2,4-dioxo-1,3-thiazolidin-5-yl)amino]phenethyl[(2*S*)-2-hydroxy-3-(4-phenoxyphenoxy)propyl]carbamate

Triethylamine (1.53, 10.97 mmol) was added into a mixture of *tert*-butyl 4-aminophenethyl[(2*S*)-2-hydroxy-3-(4-phenoxyphenoxy)propyl]carbamate (5.2 g, 10.97 mmol), 5-bromo-1,3-thiazolidine-2,4-dione (2.15 g, 10.97 mmol), and N,N-dimethylformamide (50 mL). The mixture was stirred at room temperature for 2 hours, poured into aqueous ammonium chloride and extracted with ethyl acetate. The organic extracts were dried over $MgSO_4$. Evaporation and purification by flash chromatography (hexanes/ethyl acetate 1/1) gave an off-white solid (5.1 g, 78% yield): MS *m/e* 594 $(M+H)^+$;

Analysis for: $C_{31}H_{35}N_3O_5S$ Calc'd: C, 62.72; H, 5.94; N, 7.08

Found: C, 62.07; H, 5.93; N, 7.02

Step e)

5-[4-(2-{[(2*S*)-2-Hydroxy-3-(4-phenoxyphenoxy)propyl]amino}ethyl)anilino]-1,3-thiazolidine-2,4-dione

A mixture of *tert*-butyl 4-[(2,4-dioxo-1,3-thiazolidin-5-yl)amino]phenethyl[(2*S*)-2-hydroxy-3-(4-phenoxyphenoxy)propyl]carbamate (1.5 g, 2.53 mmol), trifluoroacetic acid (5 mL) and dichloromethane (50 mL) was stirred at room temperature for 24 hours. The volatiles were removed in vacuo and the residue was triturated with ethyl ether to produce a yellow solid (1.32 g, 72% yield): mp 72-74 ^{0}C; MS *m/e* 494 $(M+H)^+$;

Analysis for: $C_{26}H_{27}N_3O_5S$ x 1.6 CF_3CO_2H Calc'd: C, 51.88; H, 4.23; N, 6.21

Found: C, 51.73; H, 4.39; N, 6.13

Example 2

5-{4-[2-({(2*S*)-3-[4-(Benzyloxy)phenoxy]-2-hydroxypropyl}amino)ethyl]anilino}-3-methyl-1,3-thiazolidine-2,4-dione

Step a) *tert*-Butyl 4-aminophenethyl{(2*S*)-3-[4-(benzyloxy)phenoxy]-2-hydroxypropyl}carbamate

Di-*tert*-butyl dicarbonate (1.2 g, 5.53 mmol) was added into a cold (0 ^{0}C) mixture of (2*S*)-1-[(4-aminophenethyl)amino]-3-[4-(benzyloxy)phenoxy]-2-propanol (2.17 g, 5.53 mmol), and tetrahydrofuran (20 mL). The mixture was stirred at 0 ^{0}C for 2 hours, poured into water, and extracted with ethyl acetate. The organic extracts were dried over $MgSO_4$. Evaporation and purification by flash chromatography (hexanes/ethyl acetate 1/1) gave a yellow oil (2.4 g, 88% yield): MS *m/e* 493 $(M+H)^+$;

Step b) 3-Methyl-1,3-thiazolidine-2,4-dione

A mixture of *N*-methylthiourea (45 g, 0.5 mol), chloroacetic acid (47 g, 0.5 mol) and water (250 mL) was refluxed for 48 hours. The mixture was cooled to room temperature and extracted with chloroform. The organic extracts were dried over $MgSO_4$. Evaporation and purification by flash chromatography (hexanes/ethyl acetate 1/2) gave an off-white solid (51.6 g, 79% yield): mp 39-41 ^{0}C; MS *m/e* 131 M^+;

Analysis for: $C_4H_5NO_2S$ Calc'd: C, 36.63; H, 3.84; N, 10.68

Found: C, 36.68; H, 3.46; N, 10.44

Step c) 5-Bromo-3-methyl-1,3-thiazolidine-2,4-dione

Bromine (2.16 mL, 42 mmol) was added dropwise into a cold (0 ^{0}C) solution of 3-methyl-1,3-thiazolidine-2,4-dione (5.5 g, 42 mmol), and acetic acid (100 mL). The mixture was

allowed to come to room temperature, and then warmed to 60 ^{0}C and stirred for 18 hours. The mixture was then poured into water and extracted with ethyl acetate. The organic layer was washed with sodium bisulfite and brine. The organic extracts were dried over $MgSO_4$. Evaporation and purification by flash chromatography (hexanes/ethyl acetate 1/3) gave a clear oil (7.2 g, 82% yield): MS *m/e* 209 M^+;

Analysis for: $C_4H_4BrNO_2S$ Calc'd: C, 22.87; H, 1.92; N, 6.67

Found: C, 22.49; H, 1.69; N, 6.52

Step d) 5-{4-[2-({(2*S*)-3-[4-(Benzyloxy)phenoxy]-2-hydroxypropyl}amino)ethyl]-anilino}-3-methyl-1,3-thiazolidine-2,4-dione

A mixture of *tert*-butyl 4-aminophenethyl{(2*S*)-3-[4-(benzyloxy)phenoxy]-2-hydroxypropyl}-carbamate (1.2 g, 2.44 mmol), 5-bromo-3-methyl-1,3-thiazolidine-2,4-dione (0.51 g, 2.44 mmol), and N,N-dimethylformamide (15 mL) was stirred at room temperature for 48 hours. The mixture was then poured into aqueous ammonium chloride and extracted with ethyl acetate. The organic extracts were dried over $MgSO_4$. Evaporation and purification by flash chromatography (hexanes/ethyl acetate 1/1) gave a light yellow solid (0.72 g, 57% yield): mp 165-167; MS *m/e* 520 $(M-H)^+$;

Analysis for: $C_{28}H_{31}N_3O_5S$ x 1 HBr Calc'd: C, 55.91; H, 5.32; N, 6.98 Found: C, 56.86; H, 5.28; N, 7.30

Example 3

5-[4-(2-{[(2*R*)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino}ethyl)anilino]-3-methyl-1,3-thiazolidine-2,4-dione

Step a) *tert*-Butyl 4-aminophenethyl[(2*R*)-2-(3-chlorophenyl)-2-hydroxyethyl]-carbamate

Di-*tert*-butyl dicarbonate (4.95 g, 22.72 mmol) was added into a cold (0 ^{0}C) mixture of (1*R*)-2-[(4-aminophenethyl)amino]-1-(3-chlorophenyl)-1-ethanol (6.6 g, 22.72 mmol), and tetrahydrofuran (30 mL). The mixture was stirred at 0 ^{0}C for 2 hours , poured into water, and extracted with ethyl acetate. The organic extracts were dried over $MgSO_4$. Evaporation and purification by flash chromatography (ethyl acetate/methyl alcohol 5/1) gave a yellow oil (7.4 g, 83% yield): MS *m/e* 390 M^+;

Analysis for: $C_{21}H_{27}ClN_2O_3$ Calc'd: C, 64.52; H, 6.96; N, 7.17

Found: C, 63.49; H, 6.49; N, 6.71

Step b) 5-[4-(2-{[(2*R*)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino}ethyl)anilino]-3-methyl-1,3-thiazolidine-2,4-di ne

A mixture of *tert*-butyl 4-aminophenethyl[(2*R*)-2-(3-chlorophenyl)-2-hydroxyethyl]-carbamate (1.9 g, 4.85 mmol), 5-bromo-3-methyl-1,3-thiazolidine-2,4-dione (1.02 g, 4.85 mmol), and N,N-dimethylformamide (15 mL) was stirred at 60 ^{0}C for 24 hours. The mixture was then poured into aqueous ammonium chloride and extracted with ethyl acetate. The organic extracts were dried over $MgSO_4$. Evaporation and purification by flash chromatography (ethyl acetate/methyl alcohol 20/1) gave an oil (1.82 g) which was taken in dichloromethane (50 mL) and treated with trifluoroacetic acid (5 mL) for 36 hours. The volatiles were then removed in vacuo and the residue was purified by flash chromatography (ethyl acetate/methyl alcohol 10/1) to give a light yellow solid (1.2 g, 60% yield): mp 129-131; MS *m/e* 420 $(M+H)^+$;

Analysis for: $C_{20}H_{22}ClN_3O_3S$ Calc'd: C, 57.20; H, 5.28; N, 10.01

Found: C, 56.99; H, 5.30; N, 9.58

Example 4

5-{4-[2-({(2*S*)-3-[4-(Benzyloxy)phenoxy]-2-hydroxypropyl}amino)ethyl]anilino}-1,3-thiazolidine-2,4-dione

Step a) (2*S*)-2-{[4-(Benzyloxy)phenoxy]methyl}oxirane

Sodium hydride (60 % in mineral oil, 2.2 g, 54.0 mmol) was added portionwise into a cold (0^0 C) mixture of 4-(benzyloxyphenol 9.26 g, 46.29 mmol) and N, N-dimethylformamide (25 mL). The mixture was stirred for 1 hour and then (2S)-(+)-oxiranylmethyl 3-nitrobenzenesulfonate (10 g, 38.5 mmol) in N, N-dimethylformamide (25 mL) was added dropwise. The new mixture was warmed up to room temperature, stirred for 18 hours, poured into water, and extracted with ethyl acetate. The organic extracts were washed with brine, and dried over $MgSO_4$. Evaporation and purification by flash chromatography (hexanes/ethyl acetate 9/1) gave a white solid (6.2 g, 62 % yield), MS m/e 256 $(M)^+$; ^{1}H NMR (DMSO-d_6 300 MHz) δ 2.68 (m, 1H), 3.28 (m, 1H), 3.74 (m, 1H), 4.21 (m, 1H), 5.02 (s, 2H), 6.91 (m, 4H), 7.40 (m, 5H);

Analysis for $C_{16}H_{16}N_4O_3$ Calc'd: C, 74.98; H, 6.29 Found: C, 74.46, H, 6.32.

Step b) (2*S*)-1-[(4-Aminophenethyl)amino]-3-[4-(benzyloxy)phenoxy]-2-propanol

This compound was prepared from (2*S*)-2-{[4-(benzyloxy)phenoxy]methyl}oxirane and 4-(2-aminoethyl)aniline as described in example 1, step b, with one modification, the mixture

was stirred in tetrahydrofuran and the product was triturated with ethyl ether to give a white solid (47 % yield): MS m/e 393 $(M+H)^+$; ^1H NMR (DMSO-d_6 300 MHz) δ 1.61 (br 2H), 2.75 (m, 3H), 2.85 (m, 3H), 3.56 (s, 2H), 3.97 (m, 2H), 3.99 (m, 1H), 5.01 (s, 2H), 6.63 (m, 2H), 6.81 (m, 2H), 6.82 (m, 2H), 6.83 (m, 2H), 7.37 (m, 5H);

Analysis for $C_{24}H_{28}N_2O_3$ Calc'd: C, 73.44; H, 7.19; N, 7.14

Found: C, 73.02; H, 7.15; N, 6.86.

Step c) *tert*-Butyl 4-aminophenethyl{(2*S*)-3-[4-(benzyloxy)phenoxy]-2-hydroxypropyl}carbamate

This compound was prepared from (2*S*)-1-[(4-aminophenethyl)amino]-3-[4-(benzyloxy)-phenoxy]-2-propanol and di-tert-butyl dicarbonate in substantially the same manner as described in example 1, step c, and was obtained as colorless oil (85 % yield), MS m/e 492 $(M)^+$; ^1H NMR (DMSO-d_6 300 MHz) δ 1.45 (s, 9H), 2.71 (m, 2H), 3.41 (m, 4H), 3.44 (m, 2H), 3.86 (m, 2H), 4.11 (m, 2H), 5.01 (s, 2H), 6.62 (d, 2H), 6.83 (d, 2H), 6.91 (m, 4H), 7.37 (m, 5H).

Step d) *tert*-Butyl (2*S*)-3-[4-(benzyloxy)phenoxy]-2-hydroxypropyl{4-[(2,4-dioxo-1,3-thiazolidin-5-yl)amino]phenethyl}carbamate

This compound was prepared from *tert*-butyl 4-aminophenethyl{(2*S*)-3-[4-(benzyl-oxy)phenoxy]-2-hydroxypropyl}carbamate and 5-bromo-1,3-thiazolidine-2,4-dione in substantially the same manner as described in example 1, step d, and was obtained as yellow foam solid (66 % yield): MS m/e 607 $(M)^+$; ^1H NMR (DMSO-d_6 300 MHz) δ 1.44 (s, 9H), 1.70 (br, 1H), 2.79 (m, 2H), 3.44 (m, 4H), 3.82 (m, 2H), 4.08 (m, 1H), 4.58 (d, 1H), 5.01 (s, 2H), 6.07 (d, 1H), 6.61 (d, 2H), 6.81 (d, 2H), 6.91 (m, 2H), 7.08 (m, 2H), 7.41 (m, 5H), 8.8 (br, 1H).

Step e) 5-{4-[2-({(2*S*)-3-[4-(Benzyloxy)phenoxy]-2-hydroxypropyl}amino) ethyl]anilino}-1,3-thiazolidine-2,4-dione

This compound was prepared from *tert*-butyl (2*S*)-3-[4-(benzyloxy)phenoxy]-2-hydroxy-propyl{4-[(2,4-dioxo-1,3-thiazolidin-5-yl)amino]phenethyl}carbamate and trifluoroacetic acid in substantially the same manner as described in example 1, step e, with one modification, the product was isolated as the free base and recrystallized from methanol, tetrahydrofuran, hexanes to give a yellow foam solid (58 % yield): mp 152 ^0C; MS m/e 508 $(M+H)^+$; ^1H NMR (DMSO-d_6 300 MHz) δ 2.68 (m, 2H), 2.81 (m, 1H), 2.88 (m, 4H), 3.85 (m, 2H), 4.00 (m, 1H), 5.02 (s, 2H), 5.45 (br, 1H), 5.99 (d, 1H), 6.59 (d, 2H), 6.66 (d, 1H), 6.84 (d, 2H), 6.86 (m, 2H) 6.92 (m, 2H), 7.28 (m, 5H), 8.80 (br, 1H);

Analysis for $C_{27}H_{29}N_3O_5$ Calc'd: C, 63.89; H, 5.76; N, 8.28
Found: C, 63.91; H, 5.90; N, 7.93.

Example 5

5-[4-(2-{[(2*S*)-2-Hydroxy-3-(4-hydroxyphenoxy)propyl]amino}ethyl)anilino]-1,3-thiazolidine-2,4-dione

Step a) *tert*-Butyl 4-aminophenethyl[(2*S*)-2-hydroxy-3-(4-hydroxyphenoxy)propyl]-carbamate

A mixture of *tert*-butyl 4-aminophenethyl{(2*S*)-3-[4-(benzyloxy)phenoxy]-2-hydroxypropyl}-carbamate (1.2 g, 2.53 mmol), 10 % Pd/C (0.1 g), and ethanol (30 mL) was hydrogenated on a Parr Shaker at 40 psi for 20 hours. The catalyst was removed by filtration through celite. Evaporation and purification by flash chromatography (hexanes/ethyl acetate/methanol 6/3/1) gave a white foam solid (0.79 g, 78 % yield): MS m/s 403 $(M+H)^+$; ^1H NMR ($CDCl_3$ 300 MHz) δ 1.45 (s, 9H), 2.73 (m, 2H), 3.41 (m, 4H), 3.58 (m, 2H), 3.86 (m, 2H), 4.09 (m, 2H), 4.95 (br, 1H), 6.60 (d, 2H), 6.75 (m, 4H), 6.93 (d, 2H).

Step b) *tert*-Butyl 4-[(2,4-dioxo-1,3-thiazolidin-5-yl)amino]phenethyl[(2*S*)-2-hydroxy-3-(4-hydroxyphenoxy)propyl]carbamate

This compound was prepared from *tert*-butyl 4-aminophenethyl[(2*S*)-2-hydroxy-3-(4-hydroxyphenoxy)propyl]carbamate and 5-bromo-1,3-thiazolidine-2,4-dione in substantially the same manner as described in example 1, step d, with one change, the compound was purified by flash chromatography (hexanes/ethyl acetate/methanol 5/4/1) and was obtained as a light yellow solid (89 % yield): MS m/e 518 $(M+H)^+$; ^1H NMR (DMSO-d_6 300 MHz) δ 1.97 (s, 9H), 3.27 (m, 1H), 3.31 (m, 5H), 3.70 (m, 2H), 3.89 (m, 1H), 5.05 (m, 1H), 6.48 (d, 1H), 6.63 (d, 2H), 6.64 (d, 2H), 6.70 (d, 2H), 6.95 (m, 3H), 8.87(s, 1H), 12.16 (s, 1H).

Step c)

5-[4-(2-{[(2*S*)-2-Hydroxy-3-(4-hydroxyphenoxy)propyl]amino}ethyl)anilino]-1,3-thiazolidine-2,4-dione

This compound was prepared from *tert*-butyl 4-[(2,4-dioxo-1,3-thiazolidin-5-yl)amino]-phenethyl[(2*S*)-2-hydroxy-3-(4-hydroxyphenoxy)propyl]carbamate and trifluoroacetic acid as described in example 1, step e, with modification, the product was isolated as the free base, extracted from the aqueous layer with n-butanol and purified by flash chromatography (hexanes/ethyl acetate/methanol 4/3/3) to give a white solid (20 % yield):

mp 165 °C; MS m/e 418 $(M+H)^+$; ^1H NMR (DMSO-d_6 300 MHz) δ 2.68 (m, 2H), 2.71 (m, 1H), 2.97 (m, 3H), 3.79 (d, 2H), 3.98 (m, 1H), 5.95 (d, 1H), 6.58 (d, 2H), 6.64 (m, 1H), 6.64 (d, 2H), 6.67 (d, 1H), 6.97 (d, 2H), 8.94 (br, 1H), other ^1H exchangeable are broad;
Analysis for $C_{20}H_{23}N_3O_5$ Calc'd: C, 57.54; H, 5.55; N, 10.07 Found: C, 57.25; H, 5.41; N, 9.82.

Example 6

5-[4-(2-{[(2*R*)-2-(3-Chlorophenyl)-2-hydroxy-ethyl]amino}ethyl)anilino]-1,3-thiazolidine-2,4-dione

Step a) (1*R*)-2-[(4-Aminophenethyl)amino]-1-(3-chlorophenyl)-1-ethanol

This compound was prepared from (S)-3-chlorostyrene oxide and 4-(2-aminoethyl)aniline as described in example 1, step b, with modification, the mixture was stirred in tetrahydrofuran. The solvent was removed and the product was triturated in ethyl ether to give a white solid (33% yield): MS m/e 291 $(M+H)^+$; ^1H NMR (DMSO-d_6 300 MHz) δ 2.65 (m 3H), 2.69 (m, 3H), 4.62 (d, 1H), 6.64 (d, 2H), 6.99 (d, 2H), 7.26 (m, 3H), 7.36 (s, 1H), all ^1H exchangeable are broad;
Analysis for $C_{16}H_{19}ClN_2O$ Calc'd: C, 66.09; H, 6.59; N, 9.63
Found: C, 66.35; H, 6.73; N, 9.80.

Step b)

***tert*-Butyl 4-aminophenethyl[(2*R*)-2-(3-chlorophenyl)-2-hydroxyethyl]carbamate.**

This compound was prepared from (1*R*)-2-[(4-aminophenethyl)amino]-1-(3-chlorophenyl)-1-ethanol and di-tert-butyl dicarbonate in substantially the same manner as described in example 1, step c, and was obtained as a colorless oil (78 % yield): MS m/e 391 $(M+H)^+$; ^1H NMR ($CDCl_3$ 300 MHz) δ 1.47 (s, 9H), 2.63 (br, 2H), 3.16 (br, 1H), 3.27 (d, 2H), 3.41 (br, 1H), 3.57 (s, 2H), 4.64 (br, 1H), 4.82 (br, 1H), 6.62 (d, 2H), 6.91 (d, 2H), 7.23 (d, 3H), 7.34(d, 1H).

Step c) *tert*-Butyl (2*R*)-2-(3-chlorophenyl)-2-hydroxyethyl{4-[(2,4-dioxo-1,3-thiazolidin-5-yl)amino]phenethyl}carbamate

This compound was prepared from *tert*-butyl 4-aminophenethyl[(2*R*)-2-(3-chlorophenyl)-2-hydroxyethyl]carbamate and 5-bromo-1,3-thiazolidine-2,4-dione in substantially the same manner as described in example 1, step d, and was obtained as a yellow foam solid (59 % yield): MS m/e 506 $(M+H)^+$; ^1H NMR (DMSO-d_6 300 MHz) δ 1.31 (d, 9H), 2.59 (m, 2H),

3.25 (m, 4H), 4.72 (br, 1H),5.56 (m, 1H), 6.48 (d, 1H), 6.60 (d, 2H), 7.01(m, 3H), 7.33 (m, 4H), 2.16 (br , 1H).

Step d) 5-[4-(2-{[(2*R*)-2-(3-Chlorophenyl)-2-hydroxy-ethyl]amino}ethyl)anilino]-1,3-thiazolidine-2,4-dione

This compound was prepared from *tert*-butyl (2*R*)-2-(3-chlorophenyl)-2-hydroxyethyl{4-[(2,4-dioxo-1,3-thiazolidin-5-yl)amino]phenethyl}carbamate and trifluoroacetic acid in substantially the same manner as described in example 1, step e, with one modification, the product was isolated as the free base, extracted from the aqueous layer with ethyl acetate and purified by flash chromatography (dichloromethane/methanol/ammonium hydroxide 9/0.99/0.01), and was obtained as a light yellow solid (25 % yield): mp 162 ^{0}C, MS m/e 406 (M+H); ^{1}H NMR (DMSO-d_6 300 MHz) δ 2.67 (m, 2H), 2.90 (m, 4H), 4.74 (m, 1H), 5.87 (br, H), 6.02 (d, 1H), 6.56 (d, 2H), 6.99 (d, 2H), 7.36 (m, 4H), 7.98 (br, 1H), other exchangeable ^{1}H are broad.

Analysis for $C_{19}H_{20}ClN_3O3S$ Calc'd: C, 56.22; H, 4.97,; N, 10.35

Found: C, 55.92; H, 4.99; N, 10.19.

Example 7

5-[4-(2-{[(2*R*)-2-Hydroxy-2-phenylethyl]amino}ethyl)anilino]-1,3-thiazolidine-2,4-dione

Step a) (1*R*)-2-[(4-Aminophenethyl)amino]-1-phenyl-1-ethanol

This compound was prepared from (S)-styrene oxide and 4-(2-aminoethyl)aniline, as described in example 1, step b, with one modification, the mixture was reflux in tetrahydrofuran. The solvent was removed and the product triturated in ethyl ether to give a white solid (32 % yield): MS m/e 257 $(M+H)^+$; ^{1}H NMR (DMSO-d_6 300 MHz) δ 2.67 (m 3H), 2.89 (m, 3H), 3.57 (br, 2H), 4.65 (m 1H), 6.64 (d, 2H), 6.99 (d, 2H), 7.27 (m, 1H), 7.34 (m, 4H), other ^{1}H exchangeable are broad.

Analysis for $C_{16}H_{20}N_2O$ Calc'd: C, 74.97; H, 7.86; N, 10.93

Found: C, 75.01; H, 7.58; N, 10.88.

Step b) *tert*-Butyl 4-aminophenethyl[(2*R*)-2-hydroxy-2-phenylethyl]carbamate

This compound was prepared from (1*R*)-2-[(4-aminophenethyl)amino]-1-phenyl-1-ethanol and di-tert-butyl dicarbonate in substantially the same manner as described in example 1, step c, and was obtained as a colorless oil (88 % % yield): MS m/e 356 $(M)^+$; ^{1}H NMR

(DMSO-d_6 300 MHz) δ 1.32 (d, 9H), 2.48 (m, 2H), 3.22 (m, 4H), 4.67 (m, 1H), 4.68 (s, 2H), 5.40 (dd, 1H), 6.46 (d, 2H), 6.77 (m, 2H), 7.29 (m, 5H).

Step c) *tert*-Butyl 4-[(2,4-dioxo-1,3-thiazolidin-5-yl)amino]phenethyl[(2*R*)-2-hydroxy-2-phenylethyl]carbamate

This compound was prepared from *tert*-butyl 4-aminophenethyl[(2*R*)-2-hydroxy-2-phenylethyl]carbamate and 5-bromo-1,3-thiazolidine-2,4-dione in substantially the same manner as described in example 1, step d, and was obtained as a light yellow solid (25 % yield): MS m/e 471 $(M)^+$; ^{1}H NMR (DMSO-d_6 300 MHz) δ 1.32 (s, 9H), 2.58 (m, 2H), 3.25 (m, 3H), 4.69 (m, 2H), 5.40 (m, 1H), 6.57 (d, 1H), 6.60 (d, 2H), 6.97 (m, 3H), 7.24 (m, 5H), 12.15 (s, 1H).

Step d)

5-[4-(2-{[(2*R*)-2-Hydroxy-2-phenylethyl]amino}ethyl)anilino]-1,3-thiazolidine-2,4-dione.

This compound was prepared from *tert*-butyl 4-[(2,4-dioxo-1,3-thiazolidin-5-yl)amino]-phenethyl[(2*R*)-2-hydroxy-2-phenylethyl]carbamate and trifluoroacetic acid in substantially the same manner as described in example 1, step e, and was obtained as a yellow solid (52 % yield): mp 55 ^{0}C; MS m/e 372 $(M+H)^+$; ^{1}H NMR (DMSO-d_6 300 MHz) δ 2.90 (m, 2H), 3.40 (m, 4H), 3.60 (br, 1H), 4.90 (d, 1H), 6.18 (br, 1H),6.48 (d, 1H), 6.65 (d, 2H), 7.08 (d, 3H), 7.33 (m, 1H), 7.39 (m, 4H), 8.85 (br, 1H),12.21 (br, 1H);

Analysis for $C_{19}H_{21}N_3O_3S$ x 1.0 CF_3CO_2H Calc'd: C, 51.90; H, 4.57; N, 8.66
Found: C, 51.21; H, 4.66; N, 8.34.

Example 8

5-[4-(2-{[(2*S*)-3-(4-Fluorophenoxy)-2-hydroxypropyl]amino}ethyl)anilino]-1,3-thiazolidine-2,4-dione

Step a) (2*S*)-2-[(4-Fluorophenoxy)methyl]oxirane

This compound was prepared from 4-fluorophenol and (2S)(+)oxiranylmethyl 3-nitrobenzenesulfonate in substantially the same manner as described in example 1, step a, and was obtained as a colorless oil (80 % yield): MS m/e 168 M^+; ^{1}H NMR (DMSO-d_6 300 MHz) δ 2.69 (m, 1H), 2.82 (m, 1H), 3.30 (m, 1H), 3.81 (m, 1H), 4.30 (m, 1H), 6.97 (d, 2H), 7.13 (d, 2H).

Step b) (2*S*)-1-[(4-Aminophenethyl)amino]-3-(4-fluorophenoxy)-2-propanol

This compound was prepared from (2*S*)-2-[(4-fluorophenoxy)methyl]oxirane and 4-(2-aminoethyl)aniline as described in example 1, step b, with one modification, the mixture was stirred at 70 °c in tetrahydrofuran. The solvent was removed in vacuo and the product was triturated with ethyl ether to give a white solid (51 % yield): MS m/e 304 M^+; ^1H NMR ($CDCl_3$ 300 MHz) δ 1.22 (br 1H), 2.71 (m, 3H), 2.84 (m, 3H), 3.40 (br, 1H), 3.57 (s, 2H), 3.90 (m, 2H), 3.99 (m, 1H), 6.64 (d, 2H), 6.83 (d, 2H), 6.95 (d, 4H), 6.98 (d, 2H);

Analysis for $C_{17}H_{21}FN_2O_2$ Calc'd: C, 67.09; H, 6.96; N, 9.20

Found: C, 66.80; H, 7.02, N, 9.12.

Step c) *tert*-Butyl 4-aminophenethyl[(2*S*)-3-(4-fluorophenoxy)-2-hydroxypropyl]-carbamate

This compound was prepared from (2*S*)-1-[(4-aminophenethyl)amino]-3-(4-fluorophenoxy)-2-propanol and di-tert-butyl dicarbonate in substantially the same manner as described in example 1, step c, and was obtained as a colorless oil (76% yield): MS m/e 405 $(M+H)^+$; ^1H NMR ($CDCl_3$ 300 MHz) δ 1.45 (s, 9H), 2.71 (m, 2H), 3.41 (m, 4H), 3.57 (m, 2H), 3.82 (m, 1H), 3.84 (m, 1H), 4.07 (m, 2H), 6.62 (d, 2H), 6.82 (d, 2H), 6.94 (m, 4H);

Analysis for $C_{22}H_{29}FN_2O_4$ Calc'd: C, 65.33; H, 7.23; N, 6.93

Found: C, 6.93; H, 7.24; N, 6.72.

Step d) *tert*-Butyl 4-[(2,4-dioxo-1,3-thiazolidin-5-yl)amino]phenethyl[(2*S*)-3-(4-fluorophenoxy)-2-hydroxypropyl]carbamate

This compound was prepared from *tert*-butyl 4-aminophenethyl[(2*S*)-3-(4-fluorophenoxy)-2-hydroxypropyl]carbamate and 5-bromo-1,3-thiazolidine-2,4-dione in substantially the same manner as described in example 1, step d, and was obtained as a yellow solid (69 % yield): MS m/e 519 $(M)^+$; ^1H NMR (DMSO-d_6 300 MHz) δ 1.28 (s, 9H), 2.85 (br, 1H), 3.08 (br, 1H), 3.31 (m, 4H), 3.78 (m, 2H),3.82 (m, 1H), 6.40 (s, 1H), 6.59 (d, 2H), 6.88 (d, 2H), 6.97 (d, 2H), 7.04 (d, 2H), all ^1H exchangeable are broad.

Step e) 5-[4-(2-{[(2*S*)-3-(4-Fluorophenoxy)-2-hydroxypropyl] amino}ethyl)anilino]-1,3-thiazolidine-2,4-dione

This compound was prepared from *tert*-butyl 4-[(2,4-dioxo-1,3-thiazolidin-5-yl)amino]-phenethyl[(2*S*)-3-(4-fluorophenoxy)-2-hydroxypropyl]carbamate and trifluoroacetic acid in substantially the same manner as described in example 1, step e, and was obtained as a yellow solid (90 %): mp 55 °C; MS m/e 420 $(M+H)^+$; ^1H NMR (DMSO-d_6 300 MHz) δ 2.81

(m, 2H), 3.03 (m, 1H), 3.20 (m, 2H), 3.95 (m, 2H), 4.01 (m, 1H), 6.48 (s, 1H), 6.63 (d, 2H), 6.96 (d, 2H), 7.07 (m, 4H), all ^{1}H exchangeable are broad.

Analysis for $C_{20}H_{22}FN_3O_4S$ x 1 CF_3COOH x 1.39 H_2O Calc'd: C, 47.26; H, 4.43; N, 7.52
Found: C, 47.04; H, 4.18; N, 7.02.

Example 9

5-[4-(2-{[(2*S*)-2-Hydroxy-3-phenoxypropyl]amino}ethyl)anilino]-1,3-thiazolidine-2,4-dione

Step a) (2*S*)-2-(Phenoxymethyl)oxirane

This compound was prepared from phenol and (2S)(+)oxiranylmethyl 3-nitrobenzenesulfonate in substantially the same manner as described in example 1, step a, and was obtained a colorless oil (73 % yield): MS m/e 150 M^+; ^{1}H NMR (DMSO-d_6 300 MHz) δ 2.69 (m, 1H), 2.82 (m, 1H), 3.31 (m, 1H), 3.81 (m, 1H), 4.28 (m, 1H), 6.95 (m, 3H), 7.27 (m, 2H).

Step b) (2*S*)-1-[(4-Aminophenethyl)amino]-3-phenoxy-2-propanol

This compound was prepared from (2*S*)-2-(phenoxymethyl)oxirane and 4-(2-aminoethyl)-aniline as described in example 1, step b, with one modification, the mixture was stirred at 70 ^{0}C in tetrahydrofuran. The solvent was removed in vacuo and the product was triturated with ethyl ether to give a white solid (46% yield): MS m/e 286 M^+, ^{1}H NMR ($CDCl_3$ 300 MHz) δ 1.54 (br 1H), 2.70 (m, 3H), 2.85 (m, 3H), 3.40 (br, 1H), 3.57 (s, 2H), 3.96 (m, 2H), 4.01 (m, 1H), 6.64 (d, 2H), 6.88 (d, 2H), 6.90 (m, 3H), 7.25 (m, 2H);

Analysis for $C_{17}H_{22}N_2O_2$ Calc'd: C, 71.30; H, 7.74; N, 9.78
Found: C, 70.83; H, 7.72; N, 9.83.

Step c) *tert*-Butyl 4-aminophenethyl[(2*S*)-2-hydroxy-3-phenoxypropyl]carbamate

This compound was prepared from (2*S*)-1-[(4-aminophenethyl)amino]-3-phenoxy-2-propanol and di-tert-butyl dicarbonate in substantially the same manner as described in example 1, step c, and was obtained as a colorless oil (84 % yield): MS m/e 387 $(M+H)^+$; ^{1}H NMR ($CDCl_3$ 300 MHz) δ 1.46 (s, 9H), 2.71 (m, 2H), 3.41 (m, 4H), 3.57 (m, 2H), 3.88 (m, 1H), 3.96 (m, 1H), 4.09 (m, 2H), 6.62 (d, 2H), 6.96 (d, 2H), 6.97 (m, 3H), 7.25 (m, 2H);

Analysis for $C_{22}H_{30}N_2O_4$ Calc'd: C, 68.37; H, 7.82; N, 7.25
Found: C, 68.08; H, 7.76; N, 6.76.

Step d) *tert*-Butyl 4-[(2,4-dioxo-1,3-thiazolidin-5-yl)amino]phenethyl[(2*S*)-2-hydroxy-3-phenoxypropyl]carbamate

This compound was prepared from *tert*-butyl 4-aminophenethyl[(2*S*)-2-hydroxy-3-phenoxypropyl]carbamate and 5-bromo-1,3-thiazolidine-2,4-dione in substantially the same manner as described in example 1, step d, and was obtained as a yellow solid (69 % yield); MS m/e 502 M^+; H NMR (DMSO-d_6 300 MHz) δ 1.33 (s, 9H), 3.01 (br, 1H), 3.08 (br, 1H), 3.31 (m, 5H), 3.82 (m, 2H), 3.89 (m, 1H), 5.12 (m, 1H), 6.49 (d, 1H), 6.60 (d, 2H), 6.88 (d, 2H), 6.98 (m, 3H), 7.28 (m, 2H),12.16 (s, 1H).

Step e) 5-[4-(2-{[(2*S*)-2-Hydroxy-3-phenoxypropyl]amino}ethyl)anilino]-1,3-thiazolidine-2,4-dione

This compound was prepared from *tert*-butyl 4-[(2,4-dioxo-1,3-thiazolidin-5-yl)-amino]phenethyl[(2*S*)-2-hydroxy-3-phenoxypropyl]carbamate and trifluoroacetic acid in substantially the same manner as described in example 1, step e, and was obtained as a yellow solid (90 % yield): mp 55 °C; MS m/e 420 $(M+H)^+$; ^{1}H NMR (DMSO-d_6 300 MHz) δ 2.81 (m, 3H), 3.98 (m, 2H), 4.15 (m, 1H), 3.98 (m, 2H), 4.15 (m, 1H), 5.86 (br, 1H) 6.50 (d, 1H), 6.63 (d, 2H), 6.96 (m, 3H), 7.09 (m, 3H), 7.29, (m, 2H), 8.60 (br, 2H), 12.21 (br, 1H);

Analysis for $C_{20}H_{23}N_3O_4S$ x $1CF_3COOH$ x 0.84 H_2O Calc'd: C, 49.75; H, 4.83; N, 7.91 Found: C, 49.07; H, 4.38; N, 7.33.

Example 10

5-[4-(2-{[(2*S*)-2-Hydroxy-3-(4-methoxyphenoxy)propyl]amino}ethyl)anilino]-1,3-thiazolidine-2,4-dione

Step a) (2*S*)-2-[(4-Methoxyphenoxy)methyl]oxirane

This compound was prepared from 4-methoxyphenol and (2S)(+)oxiranylmethyl 3-nitrobenzenesulfonate in substantially the same manner as described in example 1, step a, and was obtained as a colorless oil (64 % yield): MS m/e 180 M^+; ^{1}H NMR (DMSO-d_6 300 MHz) δ 2.78 (m, 1H) 2.85 (m, 1H), 3.38 (m, 1H), 3.71 (m, 3H), 3.80 (m, 1H), 4.25 (m, 1H), 6.98 (m, 4H).

Step b) (2*S*)-1-[(4-Aminophenethyl)amino]-3-(4-methoxyphenoxy)-2-propanol

This compound was prepared from (2*S*)-2-[(4-methoxyphenoxy)methyl]oxirane and 4-(2-aminoethyl)aniline as described in example 1, step b, with one modification, the mixture was stirred at 70 °C in tetrahydrofuran. The solvent was removed in vacuo and

the product was triturated with ethyl ether to give a white solid (67 % yield): mp 60 °C, MS m/e 317 $(M+H)^+$; ^1H NMR ($CDCl_3$ 300 MHz) δ 1.60 (br, 2H), 2.75 (m, 3H), 2.85 (m, 3H), 3.58 (br, 2H), 3.76 (s, 3H), 3.88 (m, 2H), 4.00 (m, 1H), 6.65 (d, 2H), 6.82 (s, 4H), 6.99 (d, 2H);

Analysis for $C_{18}H_{24}N_2O_3$ Calc'd: C, 68.33; H, 7.65; N, 8.85
Found: C, 68.07; H, 7.61; N, 9.13.

Step c) *tert*-Butyl 4-aminophenethyl[(2*S*)-2-hydroxy-3-(4-methoxyphenoxy)propyl]-carbamate

This compound was prepared from (2*S*)-1-[(4-aminophenethyl)amino]-3-(4-methoxyphenoxy)-2-propanol and di-tert-butyl dicarbonate in substantially the same manner as described in example 1, step c, and was obtained as a colorless oil (57 % yield): MS m/e 416 $(M+H)^+$,; ^1H NMR ($CDCl_3$ 300 MHz) δ 1.45 (s, 9H), 2.71 (m, 2H), 3.44 (m, 4H), 3.57 (br, 2H), 3.76 (s, 3H), 3.81 (m, 1H), 3.82 (m, 1H), 4.08 (m, 2H), 6.62 (d, 2H), 6.91 (s, 4H), 6.93 (d, 2H);

Analysis for $C_{23}H_{32}N_2O_5$ Calc'd: C, 66.32; H, 7.74; N, 6.72
Found: C, 66.18; H, 7.75; N, 6.64.

Step d) *tert*-Butyl 4-[(2,4-dioxo-1,3-thiazolidin-5-yl)amino]phenethyl[(2*S*)-2-hydroxy-3-(4-methoxyphenoxy)propyl]carbamate

This compound was prepared from *tert*-butyl 4-aminophenethyl[(2*S*)-2-hydroxy-3-(4-methoxyphenoxy)propyl]carbamate and 5-bromo-1,3-thiazolidine-2,4-dione in substantially the same manner as described in example 1, step d, and was obtained as a yellow solid (60 % yield); MS m/e 532 $(M+H)^+$; ^1H NMR (DMSO-d_6 300 MHz) δ 1.33 (s, 9H), 3.08 (br, 1H), 3.38 (m, 4H), 3.75 (s, 3H), 3.76 (m, 1H), 3.92 (m, 1H), 5.10 (m, 1H), 6.45 (d, 1H), 6.61 (d, 2H), 6.83 (s, 4H), 6.99 (d, 2H), 12.16 (s, 1H), other ^1H exchangeable are broad;

Analysis for $C_{26}H_{33}N_3O_7S$ Calc'd: C, 58.74; H, 6.26; N, 7.90
Found: C, 58.10; H, 6.33; N, 8.40.

Step e) 5-[4-(2-{[(2*S*)-2-Hydroxy-3-(4-methoxyphenoxy) propyl]amino}ethyl) anilino]-1,3-thiazolidine-2,4-dione

This compound was prepared from *tert*-butyl 4-[(2,4-dioxo-1,3-thiazolidin-5-yl)amino]phenethyl[(2*S*)-2-hydroxy-3-(4-methoxyphenoxy)propyl]carbamate and trifluoroacetic acid in substantially the same manner as described in example 1, step e, and was obtained as a light yellow solid (60 % yield): mp 56 °C; MS m/e 432 $(M+H)^+$; ^1H NMR (DMSO-d_6 300 MHz) δ 2.87 (m, 2H), 3.17(m, 1H), 3.19 (m, 3H), 3.70 (s, 3H), 3.90 (br 2H), 4.13 (br, 1H)

5.87 (d, 1H), 6.65 (d, 1H), 6.67 (d, 2H), 6.88 (s, 4H), 7.08 (m, 3H), 8.58 (br, 2H), 12.21 (br, 1H);

Analysis for $C_{21}H_{25}N_3O_5S$ x $1CF_3COOH$ x 0.78 H_2O Calc'd: C, 49.37; H, 4.96; N, 7.51 Found: C, 48.35; H, 4.33; N, 7.02.

Example 11

5-{4-[2-({(2*S*)-3-[3-(Benzyloxy)phenoxy]-2-hydroxypropyl}amino)ethyl]anilino}-1,3-thiazolidine-2,4-dione

Step a) (2*S*)-2-{[3-(Benzyloxy)phenoxy]methyl}oxirane

This compound was prepared from 3-benzyloxyphenol and (2S)(+)oxiranylmethyl 3-nitrobenzenesulfonate in substantially the same manner as described in example 1, step a, and was obtained as a colorless oil (47 % yield): MS m/e 256 M^+; ^1H NMR (DMSO-d_6 300 MHz), δ 2.67 (m, 1H) 2.80 (m, 1H), 3.30 (m, 1H), 3.80 (m, 3H), 4.27 (m, 1H), 5.07 (s, 2H), 6.54 (m, 1H), 6.60 (m, 2H), 7.19 (m, 1H), 7.39 (m, 5H).

Step b) (2*S*)-1-[(4-Aminophenethyl)amino]-3-[3-(benzyloxy)phenoxy]-2-propanol

This compound was prepared from (2*S*)-2-{[3-(benzyloxy)phenoxy]methyl}oxirane and 4-(2-aminoethyl)aniline as described in example 1, step b, with one modification, the mixture was stirred at 70 ^{0}C in tetrahydrofuran. The solvent was removed under vacuo and the product was triturated with ethyl ether to give a white solid (67 % yield): MS m/e 392 M^+; ^1H NMR ($CDCl_3$ 300 MHz) δ 1.6 (br, 1H), 2.69 (m, 3H), 2.85 (m, 3H), 3.30 (br, 1H), 3.55 (s, 2H), 3.92 (m, 2H), 4.00 (m, 1H), 5.03 (s, 2H), 6.59 (m, 5H), 7.00 (d, 2H), 7.19 (t, 1H), 7.40 (m, 5H);

Analysis for $C_{24}H_{28}N_2O_3$ Calc'd: C, 73.44; H, 7.19; N, 7.14

Found: C, 73.12; H, 7.06; N, 7.15.

Step c) *tert*-Butyl 4-aminophenethyl{(2*S*)-3-[3-(benzyloxy)phenoxy]-2-hydroxypropyl}carbamate

This compound was prepared from (2*S*)-1-[(4-aminophenethyl)amino]-3-[3-(benzyloxy)-phenoxy]-2-propanol and di-tert-butyl dicarbonate in substantially the same manner as described in example 1, step c, and was obtained as a light yellow oil (57 % yield): MS m/e 493 $(M+H)^+$; ^1H NMR ($CDCl_3$ 300 MHz) δ 1.58 (s, 9H), 2.71 (m, 2H), 3.41 (m, 4H), 3.55 (br, 2H), 3.84 (br, 1H), 3.92 (br, 1H), 4.09 (m, 2H), 5.04 (s, 2H), 6.59 (m, 5H), 6.93 (d, 2H), 7.19 (t, 1H), 7.38 (m, 5H);

Analysis for $C_{29}H_{36}N_2O_5$ Calc'd: C, 70.71; H, 7.37; N, 5.69
Found: C, 69.95; H, 7.20; N, 5.40.

Step d) *tert*-Butyl (2*S*)-3-[3-(benzyloxy)phenoxy]-2-hydroxypropyl{4-[(2,4-dioxo-1,3-thiazolidin-5-yl)amino]phenethyl}carbamate

This compound was prepared from *tert*-butyl 4-aminophenethyl{(2*S*)-3-[3-(benzyloxy)phenoxy]-2-hydroxypropyl}carbamate and 5-bromo-1,3-thiazolidine-2,4-dione in substantially the same manner as described in example1, step d, and was obtained as a yellow solid (83 %yield): MS m/e 608 $(M+H)^+$; ^{1}H NMR (DMSO-d_6 300 MHz) δ 1.33 (s, 9H), 2.64 (m, 2H), 3.27 (br, 1H), 3.34(m, 3H), 3.82 (m, 2H), 3.93 (m, 1H), 5.06 (s, 2H), 5.12 (m, 1H), 6.49 (m, 6H), 6.99 (m, 2H), 7.17 (t, 1H), 7.38 (m, 6 H), 12.16 (s, 1H);
Analysis for $C_{32}H_{37}N_3O_7S$ Calc'd: C, 63.24; H, 6.14; N, 6.91
Found: C, 62.50; H, 6.33; N, 7.15.

Step e) 5-{4-[2-({(2*S*)-3-[3-(Benzyloxy)phenoxy]-2-hydroxypropyl}amino)ethyl]-anilino}-1,3-thiazolidine-2,4-dione

This compound was prepared from *tert*-butyl (2*S*)-3-[3-(benzyloxy)phenoxy]-2-hydroxypropyl{4-[(2,4-dioxo-1,3-thiazolidin-5-yl)amino]phenethyl}carbamate and trifluoroacetic acid in substantially the same manner as described in example 1, step e, and was obtained as a light yellow solid (23 %yield): mp 53 ^{0}C; MS m/e 508 $(M+H)^+$,; ^{1}H NMR (DMSO-d_6 300 MHz) δ 2.86 (m, 2H), 3.06 (m, 2H), 3.20 (m, 3H), 3.96 (s, 2H), 4.15 (br 1H), 5.09 (s, 2H) 5.98 (br, 1H), 6.59 (m, 5H), 7.07 (m, 2H), 7.20 (t, 1H), 7.43 (m, 5H), 8.58 (br, 2H), 12.21 (br, 1H);
Analysis for $C_{27}H_{29}N_3O_5S$ x 1 CF_3COOH x 0.97 H_2O Calc'd: C, 54.50; H, 45.04; N, 6.76
Found: C, 54.13; H, 5.02; N, 6.10.

Example 12

5-[4-(2-{[(2*S*)-2-Hydroxy-3-(3-hydroxyphenoxy)propyl]amino}ethyl)anilino]-1,3-thiazolidine-2,4-dione

Step a) *tert*-butyl 4-aminophenethyl[(2*S*)-2-hydroxy-3-(3-hydroxyphenoxy)propyl]-carbamate

This compound was prepared from *tert*-butyl 4-aminophenethyl{(2*S*)-3-[3-(benzyloxy)phenoxy]-2-hydroxypropyl}carbamate in substantially the same manner as described in example 5, step a, and was obtained as a white solid (73 % yield): MS m/s 403 $(M+H)^+$; ^{1}H NMR (DMSO-d_6 300 MHz) δ 1.36 (s, 9H),2 .58 (t, 2H), 3.07(m, 1H), 3.28 (m, 3H), 3.74

(m, 2H), 4.83 (s, 2H), 5.07 (br, 1H), 4.95 (br, 1H), 6.32 (m, 3H), 6.45 (d, 2H), 6.80 (d, 2H), 7.02 (t, 1H), 9.34 (s, 1H).

Step b) *tert*-Butyl 4-[(2,4-dioxo-1,3-thiazolidin-5-yl)amino]phenethyl[(2*S*)-2-hydroxy-3-(3-hydroxyphenoxy)propyl]carbamate

This compound was prepared from *tert*-butyl 4-aminophenethyl[(2*S*)-2-hydroxy-3-(3-hydroxyphenoxy)propyl]carbamate and 5-bromo-1,3-thiazolidine-2,4-dione in substantially the same manner as described in example 1, step d, and was obtained as a yellow solid (89 % yield): MS m/e 518 $(M+H)^+$; H NMR (DMSO-d_6 300 MHz) δ 1.35 (s, 9H), 3.01 (br, 1H), 3.31 m, 2H), 3.76 (m, 2H), 3.94 (m, 1H), 5.11 (br, 1H), 6.32 (m, 3H), 6.50 (d, 1H), 6.62 (d, 2H), 7.03 (m, 4H), 9.36 (s, 1H), 12.18 (s, 1H).

Step c) 5-[4-(2-{[(2*S*)-2-Hydroxy-3-(3-hydroxyphenoxy)propyl] amino} ethyl)anilino]-1,3-thiazolidine-2,4-dione

This compound was prepared from *tert*-butyl 4-[(2,4-dioxo-1,3-thiazolidin-5-yl)amino]-phenethyl[(2*S*)-2-hydroxy-3-(3-hydroxyphenoxy)propyl]carbamate and trifluoroacetic acid as described in example 1, step e, with one change, he product was purified by reverse HPLC to give an off white solid (22 % yield): mp 65 ^{0}C; MS m/ 418 $(M+H)^+$; ^{1}H NMR (DMSO-d_6 300 MHz) δ 2.82 (m, 2H), 3.05 (m, 1H), 3.20 (m, 3H), 3.89 (m, 2H), 4.14 (br 1H), 5.87 (s, 1H), 6.36 (m, 3H), 6.49 (d, 1H), 6.66 (d, 2H), 7.08 (m, 4H), 8.59 (s, 2H), 9.48 (s, 1H), 12.21 (s, 1H);

Analysis for $C_{20}H_{23}N_3O_5S$ x 1 CF_3COOH x 2.47 H_2O Calc'd: C, 45.83, H, 5.03,, N, 7.29 Found: C, 45.03, H, 4.37, N, 7.24.

Example 13

5-[4-(2-{[(2*S*)-3-(9*H*-Carbazol-4-yloxy)-2-hydroxypropyl]amino}ethyl)anilino]-1,3-thiazolidine-2,4-dione

Step a) (2*S*)-1-[(4-Aminophenethyl)amino]-3-(9*H*-carbazol-4-yloxy)-2-propanol

This compound was prepared from 9*H*-carbazol-4-yl (2*S*)oxiranylmethyl ether and 4-(2-aminoethyl)aniline as described in example 1, step b, with one change, the product was purified by flash chromatography (dichloromethane/methanol 9.5/0.5) and recrystallized from tetrahydrofuran/toluene to give an off white solid (67 % yield): MS m/e 376 $(M+H)^+$,; ^{1}H NMR ($CDCl_3$ 300 MHz) δ 1.80 (br, 1H), 2.71 (m, 2H), 2.90 (m, 3H), 3.06 (m, 1H), 3.55 (br, 2H), 4.22 (m, 3H), 6.60 (d, 2H), 6.61 (d, 1H), -p0--p7.01 (d, 2H), 7.25 (d, 1H), 7.26 (m, 5H), 8.09 (s, 1H), 8.26(s, 1H);

Analysis for $C_{23}H_{25}N_3O_2$ Calc'd: C, 73.57; H, 6.71; N, 11.19
Found: C, 73.41; H, 6.82; N, 11.00.

Step b) *tert*-Butyl 4-aminophenethyl[(2*S*)-3-(9*H*-carbazol-4-yloxy)-2-hydroxypropyl]-carbamate

This compound was prepared from (2*S*)-1-[(4-aminophenethyl)amino]-3-(9*H*-carbazol-4-yloxy)-2-propanol and di-tert-butyl dicarbonate in substantially the same manner as described in example 1, step c, and was obtained as a white shiny solid (56 % yield): MS m/e 476 $(M+H)^+$; ^1H NMR (DMSO d_6 300 MHz) δ 1.35 (s, 9H), 2.50 (m, 2H), 3.28 (m, 3H), 3.49 (dd, 1H), 4.08 (m, 2H), 4.14 (m, 1H), 4.81 (s, 2H), 5.25 (d, 1H), 6.41 (d, 2H), 6.64 (d, 1H), 6.69 (m, 2H), 7.04 (d, 1H), 7.06 (t, 1H), 7.24, (t, 1H), 7.26 (t, 1H), 7.28 (d, 1H), 8.30 (dd, 1H), 11.22 (s, 1H);
Analysis for $C_{28}H_{33}N_3O_4$ Calc'd: C, 70.71; H, 6.99; N, 8.84
Found: C, 69.94; H, 7.39; N, 8.57.

Step c) *tert*-Butyl (2*S*)-3-(9*H*-carbazol-4-yloxy)-2-hydroxypropyl{4-[(2,4-dioxo-1,3-thiazolidin-5-yl)amino]phenethyl}carbamate

This compound was prepared from *tert*-butyl 4-aminophenethyl[(2*S*)-3-(9*H*-carbazol-4-yloxy)-2-hydroxypropyl]carbamate and 5-bromo-1,3-thiazolidine-2,4-dione in substantially the same manner as described in example 1, step d, and was obtained as a yellow solid (50 % yield): MS m/e 591 $(M+H)^+$; ^1H NMR (DMSO-d_6 300 MHz) δ 1.35 (s, 9H), 2.66 (t, 2H), 3.28 (m, 2H), 3.31 m, 2H), 3.39 (m, 2H), 4.10 (m, 2H), 4.20 (m, 1H), 5.29, (d, 2H), 6.45 (d, 1H), 6.57 (d, 2H), 6.64 (d, 1H), 6.98 (m, 2H), 7.06 (d, 1H), 7.08 (t, 1H), 7.26 (t, 1H), 7.28 (t, 1H), 7.44 (d, 1H), 8.31 (m, 1H), 11.24 (s, 1H), 12.17 (s 1H).

Step d) 5-[4-(2-{[(2*S*)-3-(9*H*-Carbazol-4-yloxy)-2-hydroxypropyl] amino}ethyl)anilino]-1,3-thiazolidine-2,4-dione

This compound was prepared from *tert*-butyl (2*S*)-3-(9*H*-carbazol-4-yloxy)-2-hydroxypropyl{4-[(2,4-dioxo-1,3-thiazolidin-5-yl)amino]phenethyl}carbamate and trifluoroacetic acid in substantially the same manner as described in example 1, step e, to give an off white solid (22 % yield): mp 140 ^0C; MS m/e 491 $(M+H)^+$; ^1H NMR (DMSO-d_6 300 MHz) δ 2.48 (m, 2H), 3.21 (m, 3H), 3.40 (m, 2H), 4.20 (m, 2H), 4.38 (br, 1H), 6.01 (br, 1H), 6.47 (d, 1H), 6.63 (m, 3H), 7.08 (m, 4H), 7.35 (m, 2H), 7.43 (d, 1H), 8.21 (d, 1H), 8.66 (br, 2H), 11.28 (s, 1H), 12.21 (s, 1H);

Analysis for $C_{26}H_{26}N_4O_4S$ x 1 CF_3COOH x 1 H_2O Calc'd: C, 55.63; H, 4.80; N, 10,23 Found: C, 55.77; H, 4.81; N, 8.92.

Example 14

N-{5-[(1S)-2-({4-[(2,4-Dioxo-1,3-thiazolidin-5-yl)amino]phenethyl}amino)-1-hydroxyethyl]-2-hydroxyphenyl}methanesulfonamide

Step a) N-[2-(Benzyloxy)-5-((1S)-2-bromo-1-{[*tert*-butyl(dimethyl)silyl]oxy}ethyl)-phenyl]methanesulfonamide

A solution of tert-butyldimethylsilyl triflate (11.25 mL, 5.41 mmol) in dichloromethane (10 mL) was added slowly into a cold (-78 °C) mixture of N-{2-(benzyloxy)-5-[(1S)-2-bromo-1-hydroxyethyl]phenyl}methanesulfonamide (1.93 g, 4.82 mmol), 2,6 lutidine (1.08 mL, 9.64 mmol) and dichloromethane(30 mL). The new mixture was warmed up to room temperature, stirred for 4 hours, poured into a saturated aqueous bicarbonate solution, and extracted with ethyl ether. The organic extracts were washed with brine, and dried over $MgSO_4$. Evaporation and purification by flash chromatography (hexanes/ethyl acetate 9/1) gave a white solid (1.55 g, 62 % yield): MS m/e 513M^+; ^1H NMR (DMSO-d_6 300 MHz) δ 0.10 (s, 3H), 0.16 (s, 3H), 0.84(s, 9H), 2.88 (s, 3H), 3.56 (m, 2H), 4.88 (m, 1H), 5.14 (s, 2H), 7.11 (d, 1H), 7.16 (d, 1H), 7.32 (m, 2H), 7.38 (m, 2H), 7.51(d, 2H), 8.90 (s, 1H);

Analysis for $C_{24}H_{29}N_3O_4S$ Calc'd: C, 51.35, H, 6.27, N, 2.72
Found: C, 50.02, H, 6.27, N, 2.53.

Step b) N-[5-((1S)-2-[(4-Aminophenethyl)amino]-1-{[*tert*-butyl(dimethyl) silyl]oxy} ethyl)-2-(benzyloxy)phenyl]methanesulfonamide

A mixture of N-[2-(benzyloxy)-5-((1S)-2-bromo-1-{[*tert*-butyl(dimethyl)silyl]oxy}ethyl)-phenyl]methanesulfonamide (1.55 g, 3.012 mmol), 4-(2-aminoethyl)aniline (0.53 g, 3.915 mmol), diisopropyl amine (2.4 ml, 19.60 mmol), sodium iodide (0.04 g) and tetrahydrofuran (5 mL) was stirred in a sealed flask at 100 °C for 48 hours. The mixture was cooled to room temperature, diluted with ethyl acetate, washed with aqueous brine solution, and dried over $MgSO_4$. Evaporation and purification by flash chromatography (hexanes/ethyl acetate/methanol/triethylamine 7/2/0.95/0.05) gave a white solid (1.25 g, 72 %): MS m/e 371 $(M+H)^+$; ^1H NMR (DMSO-d_6 300 MHz) δ 0.10 (s, 3H), 0.16 (s, 3H), 0.84 (s, 9H), 2.65 (m, 6H), 2.83 (s, 3H), 4.65 (m, 1H), 4.80 (s, 2H), 5.18 (s, 2H), 6.42 (d, 2H), 6.80 (d, 2H), 7.15 (s, 2H), 7.21 (s, 1H), 7.35 (m, 4H), 7.50 (d, 2H), 8.8 (br, 1H);

Analysis for $C_{29}H_{43}N_3O_4SSi$ Calc'd: C, 63.18; H, 7.54; N, 7.37

Found: C, 62.41; H, 7.45; N, 7.11.

Step c) *N*-[5-{(1*S*)-2-[(4-Aminophenethyl)amino]-1-[(triethylsilyl)oxy]ethyl}-2-(benzyloxy)phenyl]methanesulfonamide

This compound was prepared from *N*-(2-(benzyloxy)-5-{2-iodo-1-[(triethylsilyl)oxy]ethyl}-phenyl)methanesulfonamide and 4-(2-aminoethyl)aniline, as described in example 1, step b, without the present of sodium iodide to give a white solid (79 % yield): MS m/e 570 $(M+H)^+$; ^1H NMR (DMSO-d_6 300 MHz) δ 0.77 (m, 6H), 0.79 (m, 9H), 2.64 (m, 6H), 2.84 (s, 3H), 4.65 (m, 1H), 4.80 (d, 2H),5.13 (s, 2H), 6.44 (d, 2H), 6.79 (d, 2H) 7.06 (m, 3H), 7.24 (s, 1H), 7.25 (m, 1H), 7.38 (m, 2H), 7.51 (d, 2H), 8.40 (br, 1H);

Analysis for $C_{30}H_{43}N_3OSSi$ Calc'd: C, 63.18; H, 7.54; N, 7.37

Found: C, 62.20; H, 7.39; N, 7.30.

Step d) *N*-[5-{(1*S*)-2-[(4-Aminophenethyl)amino]-1-hydroxyethyl}-2-(benzyloxy)-phenyl]methanesulfonamide

A mixture of *N*-[5-{(1*S*)-2-[(4-aminophenethyl)amino]-1-[(triethylsilyl)oxy]ethyl}-2-(benzyloxy)phenyl]methanesulfonamide (2.2 g, 4.28 mmol), tetrabutylammonium fluoride: 1.0 M solution in tetrahydrofuran (20 ml) and terahydrofuran (15 ml) was stirred at ambient temperature for 48 hours, poured into water, basified with saturated bicarbonate solution, and extracted with ethyl acetate. The organic extracts were washed with aqueous brine solution, and dried over $MgSO_4$. Evaporation and recrystallization from ethyl acetate gave a white solid (1.5 g, 78 % yield): MS m/e 456 $(M+H)^+$; ^1H NMR (DMSO-d_6 300 MHz) δ 2.65 (m, 6H), 2.83 (s, 3H), 3.18 (m, 1H), 4.65 (m, 1H), 4.80 (s, 2H), 5.18 (s, 2H), 5.20 (m, 1H), 6.42 (d, 2H), 6.80 (d, 2H), 7.15 (m, 2H), 7.21 (s, 1H), 7.35 (m, 1H), 7.41 (t, 2H),7.56 (d, 2H), 8.30 (br, 1H);

Analysis for $C_{24}H_{29}N_3O_4S$ Calc'd: C, 63.22; H, 6.36; N, 9.22

Found: C, 62.57; H, 6.55; N, 8.81.

Step e) *N*-(5-{(1*S*)-2-[(4-Aminophenethyl)amino]-1-hydroxyethyl}-2-hydroxyphenyl)-methanesulfonamide

This compound was prepared from *N*-[5-{(1*S*)-2-[(4-aminophenethyl)amino]-1-hydroxyethyl}-2-(benzyloxy)phenyl]methanesulfonamide in substantially the same manner, as described in example 2, step a, with one change; the compound was recrystallized from ethanol and ethyl acetate to give a white solid (80% yield): MS m/s 366 $(M+H)^+$; ^1H NMR (DMSO d_6 300 MHz) δ 2.48 (m, 2H), 2.59 (d, 2H), 2.67 (m, 2H), 2.89 (s, 3H), 4.45 (t, 1H),

4.79 (s, 2H), 6.44 (d, 2H), 6.82 (m, 3H), 6.93 (d, 2H), 7.13 (s, 1H), all ^{1}H exchangeable are broad.

Step f) *tert*-Butyl 4-[(2,4-dioxo-1,3-thiazolidin-5-yl)amino]phenethyl((2*S*)-2-hydroxy-2-{4-hydroxy-3-[(methylsulfonyl)amino]phenyl}ethyl)carbamate

This compound was prepared from *N*-(5-{(1*S*)-2-[(4-aminophenethyl)amino]-1-hydroxyethyl}-2-hydroxyphenyl)methanesulfonamide and di-tert-butyl dicarbonate in substantially the same manner as described in example 1, step c, and was obtained as an off white solid (64 % yield): MS m/e 466 $(M+H)^+$; ^{1}H NMR (DMSO d_6 300 MHz) δ 1.35 (s, 9H), 2.88 (s, 3H), 3.01 (m, 2H), 3.03 (m, 2H), 4.57 (m, 1H), 4.81(s, 2H), 5.30 (dd, 1H), 6.45 (d, 2H), 6.80 (m, 1H), 6.82 (d, 2H), 6.94 (t, 1H), 7.13 (s, 1H), 8.59 (s, 1H), 9.69 (s, 1H).

Step g) *tert*-Butyl 4-[(2,4-dioxo-1,3-thiazolidin-5-yl)amino]phenethyl((2*S*)-2-hydroxy-2-{4-hydroxy-3-[(methylsulfonyl)amino]phenyl}ethyl)carbamate

This compound was prepared from *tert*-butyl 4-[(2,4-dioxo-1,3-thiazolidin-5-yl)-amino]phenethyl((2*S*)-2-hydroxy-2-{4-hydroxy-3-[(methylsulfonyl)amino]phenyl}ethyl)-carbamate and 5-bromo-1,3-thiazolidine-2,4-dione in substantially the same manner as described in example 1, step d, and was obtained as a yellow solid (46 % yield): MS m/e 581 $(M+H)^+$; ^{1}H NMR (DMSO-d_6 300 MHz) δ 1.35 (d, 9H), 2.49 (m, 2H), 2.88 (s, 3H), 3.27 (m, 4H), 4.59 (m, 1H), 5.28 (dd, 1H), 6.47 (d, 1H), 6.59, (d, 2H), 6.84 (m, 1H), 6.96 (m, 3H), 7.14 (t, 1H), 7.23 (m, 1H), 8.61 (s, 1H), 9.71 (s, 1H), 12.23 (s, 1H).

Step h) *N*-{5-[(1*S*)-2-({4-[(2,4-Dioxo-1,3-thiazolidin-5-yl)amino]phenethyl}amino)-1-hydroxyethyl]-2-hydroxyphenyl}methanesulfonamide

This compound was prepared from *tert*-butyl 4-[(2,4-dioxo-1,3-thiazolidin-5-yl)amino]phenethyl((2*S*)-2-hydroxy-2-{4-hydroxy-3-[(methylsulfonyl)amino]phenyl} ethyl)carbamate and trifluoroacetic acid in substantially the same manner as described in example 1, step e, to give an off white solid (22 % yield): mp 130 °C; MS m/e 481 $(M+H)^+$; ^{1}H NMR (DMSO-d_6 300 MHz) δ 2.83 (m, 2H), 2.95 (m, 3H), 3.09 (m, 1H), 3.10 (br, 3H), 4.78 (d, 1H), 6.7 (s, 1H), 6.47 (d, 1H), 6.65 (d, 2H), 6.89 (d, 1H), 7.05 (m, 4H), 7.23 (s, 1H), 8.57 (br, 2H), 8.74 (s, 1H), 9.96 (s, 1H), 12.20 (s, 1H);

Analysis for $C_{20}H_{24}N_4O_6S_2$ x 1 CF_3COOH x 1.87 H_2O Calc'd: C, 55.63; H, 4.80; N, 10,23 Found: C, 55.77; H, 4.81, N, 8.92.

Example 15

5-[4-(2-{[(2*S*)-3-(1-Benzofuran-5-yloxy)-2-hydroxypropyl]amino}ethyl)anilino]-1,3-thiazolidine-2,4-dione

Step a) 4-Hydroxybenzofuran.

A solution of boron tribromide: 1.0 M solution in methylene chloride (95 ml) was added slowly into a cold (-78^{0}C) solution of 5-methoxybezofuran (10 g, 67.5 mmol) in dichloromethane(100 mL). The new mixture was warmed up to room temperature, stirred for 18 hours, poured into a saturated aqueous bicarbonate solution, and extracted with ethyl acetate. The organic extracts were washed with brine, dried over $MgSO_4$. Evaporation and purification by flash chromatography (hexanes/ethyl acetate 9/1) gave a white solid (5.9 g, 65 %): MS m/e 133 $(M-H)^+$; ^{1}H NMR (DMSO-d_6 300 MHz) δ 6.72 (m, 1H), 6.78 (d, 1H), 6.94 (d, 1H), 7.35 (d, 1), 781, (s, 1H), 8.18 (s, 1H).

Step b) 1-Benzofuran-5-yl (2*R*)-oxiranylmethyl ether

This compound was prepared from 4-hydroxybenzofuran and (2S)-(+)oxiranylmethyl 3-nitrobenzenesulfonate in substantially the same manner as described in example 1, step a, and was obtained as colorless oil (38 % yield): MS m/e 190 $(M)^+$,; ^{1}H NMR (DMSO-d_6 300 MHz): δ 2.71 (m, 1H) 2.85 (m, 1H), 3.34 (m, 1H), 3.85 (m, 1H), 4.33 (m, 1H), 6.88 (s, 1H), 6.94 (d, 1H), 7.16 (s, 1H), 7.48 (d, 1H), 7.94 (s, 1H).

Step c) (2*S*)-1-[(4-Aminophenethyl)amino]-3-(1-benzofuran-5-yloxy)-2-propanol

This compound was prepared from 1-benzofuran-5-yl (2*R*)oxiranylmethyl ether and 4-(2-aminoethyl)aniline as described in example 1, step b, with one modification, the mixture was stirred at 70 ^{0}C in tetrahydrofuran for 48 hours. The solvent was removed in vacuo and the product was triturated with ethyl ether to give a white solid (25 % yield): MS m/e 326 M^+; ^{1}H NMR ($CDCl_3$ 300 MHz) δ 2.61 (br, 1H), 2.83 (m, 6H), 3.57 (s, 3H), 4.01 (m, 3H), 6.63 (m, 2H), 6.65 (s, 1H), 6.88 (m, 1H), 6.98 (m, 2H), 7.00 (m, 1H), 7.25 (d, 1H), 7.39 (s, 1H);

Analysis for $C_{19}H_{22}N_2O_3$ Calc'd: C, 69.92; H, 6.79; N, 8.58 Found: C, 69.74; H, 6.77; N, 9.10.

Step d) *tert*-Butyl 4-aminophenethyl[(2*S*)-3-(1-benzofuran-5-yloxy)-2-hydroxypropyl]-carbamate

This compound was prepared (2*S*)-1-[(4-aminophenethyl)amino]-3-(1-benzofuran-5-yl-oxy)-2-propanol and di-tert-butyl dicarbonate in substantially the same manner as described in example 1, step c, and was obtained as a light yellow oil (48 % yield): MS

m/e 426 $(M)^+$; ^1H NMR ($CDCl_3$ 300 MHz) δ 1.44 (s, 9H), 2.72 (m, 2H), 3.44 (m, 4H), 3.60 (br, 2H), 3.90 (br, 1H),3.98 (br, 1H), 4.09 (m, 2H), 6.60 (m, 2H), 6.70 (s, 1H), 6.92 (m 3H), 7.05 (s, 1H), 7.40 (d, 1H), 7.60 (s, 1h).

Step e) *tert*-Butyl (2*S*)-3-(1-benzofuran-5-yloxy)-2-hydroxypropyl{4-[(2,4-dioxo-1,3-thiazolidin-5-yl)amino]phenethyl}carbamate

This compound was prepared from *tert*-butyl 4-aminophenethyl[(2*S*)-3-(1-benzofuran-5-yloxy)-2-hydroxypropyl]carbamate and 5-bromo-1,3-thiazolidine-2,4-dione in substantially the same manner as described in example 1, step d, and was obtained as yellow solid (50 % yield), MS m/e 591 $(M+H)^+$, ^1H NMR (DMSO-d_6 300 MHz) δ 1.35 (s, 9H), 2.66 (m, 3H), 3.40 (m, 3H), 3.98 (m, 3H), 5.14 (br, 1H), 6.59 (d, 2H), 6.61 (d, 1H), 6.85 (m, 2H), 6.99 (m, 3H), 7.13 (s, 1H), 7.45 (d, 1H),7.91 (s, 1H), 12.16 (br, 1H).

Step f) 5-[4-(2-{[(2*S*)-3-(1-Benzofuran-5-yloxy)-2-hydroxypropyl]amino} ethyl)anilino]-1,3-thiazolidine-2,4-dione

This compound was prepared from *tert*-butyl (2*S*)-3-(1-benzofuran-5-yloxy)-2-hydroxypropyl{4-[(2,4-dioxo-1,3-thiazolidin-5-yl)amino]phenethyl}carbamate and trifluoroacetic acid as described in example 1, step e, with one change, the product was purified by reverse HPLC to give an off white solid (10 % yield): mp 50 ^0C; MS m/e 442 $(M+H)^+$; ^1H NMR (DMSO-d_6 300 MHz) δ 2.86 (m, 2H), 3.23 (m, 4H), 3.99 (m, 2H), 4.16 (m, 1H), 5.85 (br, 1H), 6.48 (d, 1H), 6.65 (d, 2H), 6.87 (m, 2H), 7.07 (m, 3H), 7.18 (s, 1H), 7.48 (d, 1H), 7.94 (s, 1H), 8.60 (br, 2H), 12.20 (s, 1H);

Analysis for $C_{22}H_{23}N_3O_5S$ x 1.3 CF_3COOH x 1.25 H_2O Calc'd: C, 48.21; H, 4.16; N, 6.86 Found: C, 46.44; H, 4.16; N, 6.86.

Example 16

5-[4-(2-{[(2*S*)-3-(4-Butoxyphenoxy)-2-hydroxypropyl]amino}ethyl)anilino]-1,3-thiazolidine-2,4-dione

Step a) (2*R*)-2-[(4-Butoxyphenoxy)methyl]oxirane

This compound was prepared from 4-butoxyphenol and (2S)-(+)oxiranylmethyl 3-nitrobenzenesulfonate in substantially the same manner as described in example 1, step a, and was obtained as a colorless oil (51 % yield): MS m/e 222 M^+; ^1H NMR (DMSO-d_6 300 MHz): δ 0.90 (t, 3H), 1.41 (m, 2H), 1.64 (m, 2H), 2.65 (m, 1H), 2.80 (m, 1H), 3.29 (m, 1H), 3.75 (m, 1H), 3.85 (t, 2H), 4.24 (dd, 1H), 6.87 (dd, 4H);

Analysis for $C_{13}H_{18}O_3$ Calc'd: C, 70.25; H, 8.16 Found: C, 69.94 H, 8.13.

Step b) (2*S*)-1-[(4-Aminophenethyl)amino]-3-(4-butoxyphenoxy)-2-propanol

This compound was prepared from (2*R*)-2-[(4-butoxyphenoxy)methyl]oxirane and 4-(2-aminoethyl)aniline as described in example 1, step b, with one modification, the mixture was stirred at 70 ^{0}C in tetrahydrofuran for 48 hours. The solvent was removed in vacuo and the product was triturated with ethyl ether to give a white solid (49 % yield): MS m/e 286 $(M)^+$; ^{1}H NMR ($CDCl_3$ 300 MHz) δ 0.96 (t, 3H) 1.46 (m, 2H), 1.75 (m, 2H), 1.85 (br, 1H), 2.69 (m, 3H), 2.82 (m, 3H), 3.57 (br, 2H), 3.88 (m, 5H), 3.98 (m, 1H), 6.61 (d, 2H), 6.81 (s, 4H), 6.99 (d, 2H);

Analysis for $C_{21}H_{30}N_2O_3$ Calc'd: C, 70.29; H, 7.79; N, 7.81

Found: C, 70.20; H, 8.32; N, 7.86.

Step c) *tert*-Butyl 4-aminophenethyl[(2*S*)-3-(4-butoxyphenoxy)-2-hydroxypropyl]-carbamate

This compound was prepared from (2*S*)-1-[(4-aminophenethyl)amino]-3-(4-butoxy-phenoxy)-2-propanol and di-tert-butyl dicarbonate in substantially the same manner as described in example 1, step c, and was obtained as a colorless oil (66 % yield), MS m/e 459 $(M+H)^+$; ^{1}H NMR ($CDCl_3$ 300 MHz) δ 0.96 (t, 3H), 1.45 (s, 9H), 1.46 (m, 2H), 1.74 (m, 2H), 2.70 (m, 2H), 3.39 (m, 4H), 3.57 (br, 2H), 3.88 (m, 1H), 3.90 (m, 3H), 4.09 (br, 2H), 6.60 (d, 2H), 6.81 (s, 4H), 6.93 (d, 2H);

Analysis for $C_{26}H_{38}N_2O_5$ x 0.6 $C_4H_8O_2$ Calc'd: C, 66.66; H, 7.68; N, 5.66

Found: C, 65.32; H, 7.95; N, 5.69.

Step d) *tert*-Butyl (2*S*)-3-(4-butoxyphenoxy)-2-hydroxypropyl{4-[(2,4-dioxo-1,3-thiazolidin-5-yl)amino]phenethyl}carbamate

This compound was prepared from *tert*-butyl 4-aminophenethyl[(2*S*)-3-(4-butoxyphenoxy)-2-hydroxypropyl]carbamate and 5-bromo-1,3-thiazolidine-2,4-dione in substantially the same manner as described in example 1, step d, and was obtained as a light yellow solid (63 % yield): MS m/e 573 $(M)^+$; ^{1}H NMR (DMSO-d_6 300 MHz) δ 0.93 (t, 3H), 1.35(s, 9H), 1.42 (m, 2H), 1.67 (m, 2H), 2.65 (m, 1H), 3.05 (br, 1H), 3.29 (m, 2H), 3.35 (m, 2H), 3.76 (m, 2H), 3.88 (m, 2H), 5.10 (br, 1H), 6.47 (d, 1H), 6.83 (d, 2H), 6.99 (s, 4H), 7.01 (m, 3H), 12.16 (s, 1H);

Analysis for $C_{29}H_{39}N_3O_3S$ Calc'd: C, 60.,71; H, 6.85; N, 7.

Found: C, 60.44; H, 6.83; N,7.32.

Step e) 5-[4-(2-{[(2*S*)-3-(4-Butoxyphenoxy)-2-hydroxypropyl]amino}ethyl)anilino]-1,3-thiazolidine-2,4-dione

This compound was prepared from *tert*-butyl (2*S*)-3-(4-butoxyphenoxy)-2-hydroxypropyl-{4-[(2,4-dioxo-1,3-thiazolidin-5-yl)amino]phenethyl}carbamate and trifluoroacetic acid in substantially the same manner as described in example 1, step e, and was obtained as a light yellow solid (72 % yield): mp 65 ^{0}C; MS m/e 447 $(M+H)^+$; ^{1}H NMR (DMSO-d_6 300 MHz) δ 0.93 (t, 3H), 1.41 (m, 2H), 1.64 (m, 2H), 2.85 (m, 3H), 3.01 (br, 1H), 3.89 (m, 1H), 4.09 (br, 1H), 5.84 (br, 1H), 6.50 (d, 1H), 6.65 (d, 2H), 6.85 (s, 4H), 7.06 (m, 3H), 8.56 (br, 2H), 12.21 (br, 1H);

Analysis for $C_{26}H_{31}N_3O_5S$ x 1 CF_3COOH Calc'd: C, 43.14,; H, 5.49; N, 7.15
Found: C, 52.60; H 5.70; N, 6.63.

Example 17

5-[4-(2-{[(2*S*)-2-Hydroxy-3-phenoxypropyl]amino}ethyl)(methyl)anilino]-1,3-thiazolidine-2,4-dione.

Step a) (2*S*)-1-[(4-Nitrophenethyl)amino]-3-phenoxy-2-propanol

This compound was prepared from (*S*)-2-(phenoxymethyl)oxirane (Example 6, step a) and 4-nitrophenylethylamine as described in example 1, step b, with one modification, the mixture was stirred at 70 ^{0}C, and was obtained as an off white solid (73 % yield): MS m/e 316 M^+; ^{1}H NMR ($CDCl_3$ 300 MHz), 1.85 (br, 1H), 3.0 (m, 6H), 3.98 (d, 2H), 4.03 (m, 1H), 6.85 (d, 2H), 6.99 (t, 1H), 7.25 (m, 3H), 7.40 (d, 2H), 8.18 (d, 2H).

Step b) (1*S*)-2-[(*tert*-Butoxycarbonyl)(4-nitrophenethyl)amino]-1-(phenoxymethyl) ethyl *tert*-butyl carbonate

This compound was prepared from (2*S*)-1-[(4-nitrophenethyl)amino]-3-phenoxy-2-propanol and di-tert-butyl dicarbonate as described in example 1, step c, with one modification, the reaction was conducted in acetonitrile in the presence of 4-(dimethylamino)pyridine, and the product was obtained as a colorless oil (68 % yield): MS m/e 516 $(M+H)^+$; ^{1}H NMR ($CDCl_3$ 300 MHz) δ 1.44 (s, 9H), 1.50 (s, 9H), 3.0 (br, 2H), 3.30 (br, 1H), 3.59 (br, 3H), 4.01 (m, 2H), (m, 2H), 5.08 (m, 1H), 6.85 (d, 2H), 6.97 (t, 1H), 7.25 (m, 4H), 8.18 (d, 2H);

Analysis for $C_{27}H_{36}N_2O_8$ Calc'd: C, 62.78; H, 7.02; N, 5.42
Found: C, 61.91; H, 7.03; N, 5.32.

Step c) (1*S*)-2-[(4-Aminophenethyl)(*tert*-butoxycarbonyl)amino]-1-(phenoxymethyl)-ethyl *tert*-butyl carbonate

A mixture of compound from 1*S*)-2-[(*tert*-butoxycarbonyl)(4-nitrophenethyl)amino]-1-(phenoxymethyl)ethyl *tert*-butyl carbonate (3.3 g, 6.38 mmol), 10 % Pd/C (0.1 g), and ethanol (35 mL) was hydrogenated on a Parr Shaker at 40 psi for 4 hours. The catalyst was removed by filtration through celite. Evaporation of the filtrate gave a colorless oil (93 % yield): MS m/s 486 $(M+H)^+$; ^1H NMR ($CDCl_3$ 300 MHz) δ 1.24 (d, 18H), 2.72 (m, 2H), 3.38 (br, 3H), 3.59 (br, 3H), 4.02 (br, 2H), 5.04 (br, 1H), 6.61 (d, 2H), 6.88 (d, 2H), 6.97 (m 3H), 7.26 (d, 2H).

Step d) (1*S*)-2-((*tert*-Butoxycarbonyl){4-[(2,2,2-trifluoroacetyl)amino]phenethyl}-amino)-1-(phenoxymethyl)ethyl *tert*-butyl carbonate

A mixture of compound from(1*S*)-2-[(4-aminophenethyl)(*tert*-butoxycarbonyl)amino]-1-(phenoxymethyl)ethyl *tert*-butyl carbonate (2.90 g, 5.95 mmol), S-ethyl-trifluorothioacetate (2.38 ml, 18.44 mmol) and methanol (21 mL) was stirred at ambient temperature for 18 hours. Evaporation and purification by flash chromatography (hexanes/ethyl acetate/-methanol 7/2.5/0.5) to give a white solid (62 % yield): MS m/e 581 $(M-H)^+$; ^1H NMR (DMSO-d_6 300 MHz) δ 1.47 (s, 18H), 2.86 (m, 2H), 3.32 (br, 1H), 3.45 (br, 2H), 3.46 (br, 1H), 4.02 (br, 2H), 5.11 (br, 1H), 6.88 (d, 2H), 6.97 (t, 1H), 7.22 (m, 4H), 7.48 (d, 2H), 7.80 (s, 1H)

Analysis for $C_{29}H_{37}F_3N_2O_7$ Calc'd: C, 59.78; H, 6.40; N, 4.81

Found: C, 59.49; H, 6.42; N, 4.61.

Step e) (1*S*)-2-((*tert*-Butoxycarbonyl){4-[methyl(2,2,2-trifluoroacetyl)amino]-phenethyl}amino)-1-(phenoxymethyl)ethyl *tert*-butyl carbonate

This compound was prepared from (1*S*)-2-((*tert*-butoxycarbonyl){4-[(2,2,2-trifluoro-acetyl)amino]phenethyl}amino)-1-(phenoxymethyl)ethyl *tert*-butyl carbonate and methyl iodide as described in example 1, srep a, and was obtained as a colorless oil. MS m/e 596 $M)^+$; ^1H NMR (t300 MHz) δ 1.48 (s, 18H), 2.93 (br, 2H), 3.30 (m, 1H), 3.34 s, 3H), 3.50 (m, 3H), 4.10 (br, 2H), 4.05 (m, 1H), 5.15 (br, 1H), 6.90 (d, 2H), 7.15 (t, 1H), 7.25 (d, 2H), 7.28 (m, 4H).

Step f) (1*S*)-2-{(*tert*-Butoxycarbonyl)[4-(methylamino)phenethyl]amino}-1-(phenoxymethyl)ethyl *tert*-butyl carbonate

A mixture of (1*S*)-2-((*tert*-butoxycarbonyl){4-[methyl(2,2,2-trifluoroacetyl)amino]phenethyl}-amino)-1-(phenoxymethyl)ethyl *tert*-butyl carbonate (2.1g, 3.52 mmol), 40% aqueous

solution of potassium hydroxide (15 mL) and dioxane (10 mL) was stirred at ambient temperature for 18 hours. The product was extracted with dichloromethane, and dried over K_2CO_3. Evaporation and purification by flash chromatography (hexanes/dichloromethane/methanol (9/0.7/0.3) gave a light yellow oil (1.62 g, 92 % yield): MS m/e 500 M^+; ^1H NMR ($CDCl_3$ 300 MHz), δ 1.48 (s, 18H), 2.93 (br, 2H), 3.30 (m, 1H), 3.34 s, 3H), 3.50 (m, 3H), 4.05 (m, 1H), 4.10 (br, 2H),5.15 (br, 1H), 6.56 (d, 2H), 6.86 (d, 2H), 6.99 (m, 4H), 7.02 (m, 4H).

Step g) (1*S*)-2-((*tert*-Butoxycarbonyl){4-[(2,4-dioxo-1,3-thiazolidIn-5-yl)(methyl)-amino]phenethyl}amino)-1-(phenoxymethyl)ethyl *tert*-butyl carbonate

This compound was prepared from (1*S*)-2-{(*tert*-butoxycarbonyl)[4-(methylamino)phenethyl]amino}-1-(phenoxymethyl)ethyl *tert*-butyl carbonate and 5-bromo-1,3-thiazolidine-2,4-dione in substantially the same manner as described in example 1, step d, and was obtained as an off white solid (50 % yield): MS m/e 616 $(M+)^+$; ^1H NMR (DMSO-d_6 300 MHz) δ 1.38 (s, 18H), 2.67 (t, 2H), 2.74 (s, 3H), 3.29 (m, 2H), 3.42 (m, 2H), 4.01 (m, 1H), 4.02 (m, 1H), 5.02 (br, 1H), 6.90 (m, 6H), 7.07 (d, 2H), 7.28 (t, 2H), 12.61 (s, 1H);

Analysis for $C_{31}H_{41}N_3O_8S$ Calc'd: C, 60.47; H, 6.71; N, 6.82

Found: C, 59.23; H, 6.60; N, 6.38.

Step h) 5-[4-(2-{[(2*S*)-2-Hydroxy-3-phenoxypropyl]amino}ethyl)(methyl)anilino]-1,3-thiazolidine-2,4-dione.

This compound was prepared from (1*S*)-2-((*tert*-butoxycarbonyl){4-[(2,4-dioxo-1,3-thiazolidin-5-yl)(methyl)amino]phenethyl}amino)-1-(phenoxymethyl)ethyl *tert*-butyl carbonate and trifluoroacetic acid in substantially the same manner as described in example 1, step e, and was obtained as a white solid (31 % yield): mp 58 ^0C; MS m/e 416 $(M+H)^+$; ^1H NMR (DMSO-d_6 300 MHz) δ 2.76 (m, 3H), 2.88 (m, 2H), 3.03 (m, 1H), 3.22 (m, 2H), 3.90 (m, 2H), 4.41 (br, 1H), 5.88 (br, 1H), 6.94 (m, 6H), 7.16 (d, 2H), 7.29 (d, 2H), 8.64 (s, 2H), 12.36 (s, 1H);

Analysis for $C_{17}H_{18}F_3N_2O_3S$ x 1.3 CF_3COOH x 1 H_2O Calc'd: C, 48.68; H, 4.52; N, 7.22

Found: C, 48.93; H 4.59; N, 7.33.

Example 18

5-[4-(2-{[(2*R*)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino}propyl)anilino]-1,3-thiazolidine-2,4-dione

Step a) (1*R*)-2-{[2-(4-Aminophenyl)-1-methylethyl]amino}-1-(3-chlorophenyl)-1-ethanol

This compound was prepared from (2*R*)-2-(3-chlorophenyl)oxirane and 2-(4-aminophenyl)-1-methylethylamine as described in example 1, step b, with one modification, the mixture was stirred in tetrahydrofuran at 70 ^{0}C for 48 hours. The product was triturated ethyl ether to give a white solid (48 % yield): MS m/e 305 $(M+H)^+$; ^{1}H NMR (DMSO-d_6 300 MHz) δ 0.86 (m, 3H),2.23 (m, 1H), 2.53 (m, 2H), 2.66 (m, 2H),4.58 (m, 1H), 5.30 (d, 2H), 5.40 (br, 1H), 6.45 (m, 2H), 6.77 (m, 2H), 7.26(m, 4H).

Step b) *tert*-butyl 2-(4-Aminophenyl)-1-methylethyl[(2*R*)-2-(3-chlorophenyl)-2-hydroxyethyl]carbamate

This compound was prepared from 1*R*)-2-{[2-(4-aminophenyl)-1-methylethyl]amino}-1-(3-chlorophenyl)-1-ethanol and di-tert-butyl dicarbonate in substantially the same manner as described in example 1, step c, and was obtained as a colorless oil (68 % yield): MS m/e 405 M^+.

Step c) *tert*-Butyl (2*R*)-2-(3-chlorophenyl)-2-hydroxyethyl(2-{4-[(2,4-dioxo-1,3-thiazolidin-5-yl)amino]phenyl}-1-methylethyl)carbamate

This compound was prepared from *tert*-butyl 2-(4-aminophenyl)-1-methylethyl[(2*R*)-2-(3-chlorophenyl)-2-hydroxyethyl]carbamate and 5-bromo-1,3-thiazolidine-2,4-dione in substantially the same manner as described in example 1, step d, and was obtained as a yellow solid (82 % yield): MS m/e 520/522 $(M + H)^+$;

Analysis for $C_{25}H_{30}ClN_3O_5S$ Calc'd: C, 57.74; H, 5.81; N, 8.08

Found: C, 57.06; H, 5.88; N, 7.99.

Step d) 5-[4-(2-{[(2*R*)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino}propyl)anilino]-1,3-thiazolidine-2,4-dione

This compound was prepared from *tert*-butyl (2*R*)-2-(3-chlorophenyl)-2-hydroxyethyl(2-{4-[(2,4-dioxo-1,3-thiazolidin-5-yl)amino]phenyl}-1-methylethyl)carbamate and trifluoroacetic acid in substantially the same manner as described in example 1, step e, and was obtained as a white solid (21 % yield): mp 83-85 ^{0};, MS m/e 420/422 $(M+H)^+$; ^{1}H NMR (DMSO-d_6 300 MHz) δ 1.12 (t, 3H), 3.07 (m, 3H), 4.01 (br, 1H), (m, 2H), 4.93 (t, H), 6.49

(d, 1H), 6.63 (m, 2H), 7.06 (m, 3H), 7.43 (m, 3H), 7.44 (s, 1H), 8.73 (br, 2H), 12.22 (s, 1H);

Analysis for $C_{20}H_{22}ClN_3O_3S$ x 1.8 CF_3COOH x 0.46 H_2O Calc'd: C, 44.70; H, 3.90; N, 6.62
Found: C, 44.60; H, 3.79; N, 6.58.

Example 19

5-{4-[2-({(2*R*)-2-Hydroxy-3-[(2-oxo-2,3-dihydro-1*H*-benzimidazol-4-yl)oxy]propyl}-amino)ethyl]anilino}-1,3-thiazolidine-2,4-dione

Step a) 2-Nitro-6-[(2*R*)-oxiranylmethoxy]aniline

A mixture of 2-amino-3-nitrophenol (25.3 g, 164.1 mmol), (2S)-(+)oxiranylmethyl 3-nitrobenzenesulfonate (42.5, 164.1 mmol), potassium carbonate (29 g, 209.8 mmol) and acetone (300 mL) was refluxed for 6 hours. After cooling to room temperature, the mixture was filtered, and the filtrate was removed in vacuo. The residue was partitioned between dichloromethane and water. The organic layer was washed with aqueous bicarbonate, and dried over $MgSO_4$. Evaporation and purification by recrystallization from dichloromethane/hexanes gave an orange colored solid (31 g, 90 % yield): MS m/e 210 $(M)^+$;

Analysis for $C_9H_{10}N_2O_4$ Calc'd: C, 51.43; H, 4.80; N, 13.33
Found: C, 50.92; H 4.57; N, 13.41.

Step b) (2*R*)-1-(2-Amino-3-nitrophenoxy)-3-[(4-aminophenethyl)amino]-2-propanol

This compound was prepared from 2-nitro-6-[(2*R*)oxiranylmethoxy]aniline and 4-(2-aminoethyl)aniline as described in example 1, step b, with one modification, the mixture was stirred in tetrahydrofuran at 70 ^{0}C for 24 hours, and the product was triturated with dichloromethane to give a yellow solid (63 % yield): MS m/e 346 $(M)^+$; ^{1}H NMR (DMSO-d_6 300 MHz) δ 1.87 (br 1H), 2.50 (m, 2H), 2.67 (m, 4H), 3.82 (m, 1H), 3.84 (m, 1H), 4.01 (m, 1H), 4.81 (s, 2H), 5.24 (s, 1H),6.46 (d, 2H), 6.59 (m, 1H), 6.86 (d, 2H), 7.02 (d, 1H), 7.22 (s, 2H), 7.59 (d, 1H);

Analysis for $C_{17}H_{22}N_4O_4$ Calc'd: C, 58.95; H, 6.4; N, 16.17
Found: C, 58.30; H, 7.15; N, 15.61.

Step c) *tert*-Butyl (2*R*)-3-(2-amino-3-nitrophenoxy)-2-hydroxypropyl(4-aminophenethyl)carbamate

This compound was prepared from (2*R*)-1-(2-amino-3-nitrophenoxy)-3-[(4-aminophenethyl)amino]-2-propanol and di-tert-butyl dicarbonate as described in example 1, step c, to

give a yellow solid (77 % yield): MS m/e 447 $(M)^+$; ^1H NMR (DMSO-d_6 300 MHz) δ 1.36 (s 9H), 2.59 (m, 2H), 3.24 (m, 4H), 3.79 (m, 1H), 4.00 (m, 2H), 4.81 (s, 2H), 5.35 (d, 1H), 6.46 (d, 2H), 6.55 (t, 1H), 6.81 (d, 2H), 7.00 (d, 1H), 7.21 (s, 2H), 7.57 (d, 1H);

Analysis for $C_{22}H_{30}N_4O_5$ Calc'd: C, 59.18; H, 6.77; N, 12.55

Found: C, 59.32; H, 6.65; N, 12.81.

Step d) *tert*-Butyl 4-aminophenethyl[(2*R*)-3-(2,3-diaminophenoxy)-2-hydroxypropyl]-carbamate

This compound was prepared from *tert*-butyl (2*R*)-3-(2-amino-3-nitrophenoxy)-2-hydroxypropyl(4-aminophenethyl)carbamate as described in EP 0764640 to give a yellow solid (70 % yield): MS m/e 417 $(M)^+$; ^1H NMR (DMSO-d_6 300 MHz) δ 1.37 (s 9H), 2.57 (m, 2H), 3.06 (m, 1H), 3.30 (m, 3H), 3.63 (m, 1H), 3.68 (m, 1H), 3.98 (m, 1H), 4.16 (br, 2H), 4.45 (br, 2H), 4.82 (br, 2H), 5.13 (d, 1H), 6.11 (d, 1H), 6.19 (d, 1H), 6.32 (t, 1H), 6.45 (d, 2H), 6.79 (d, 2H);

Analysis for $C_{22}H_{32}N_4O_4$ Calc'd: C, 63.44; H, 7.74; N, 13.45

Found: C, 62.17; H, 7.53; N, 13.25.

Step d) *tert*-Butyl 4-aminophenethyl{(2*R*)-2-hydroxy-3-[(2-oxo-2,3-dihydro-1*H*-benzimidazol-4-yl)oxy]propyl}carbamate

A mixture of *tert*-butyl 4-aminophenethyl[(2*R*)-3-(2,3-diaminophenoxy)-2-hydroxypropyl]-carbamate (1.0 g, 2.4 mmol),1,1-carbonyldiimidazole (0.52 g, 3.2 mmol) and dioxane (20 mL) was stirred at ambient temperature for 18 hours. The solvent was removed in vacuo and the residue was purified by flash chromatography (hexanes/dichloromethane/ethanol 4/4/2) to give an off white solid (0.28g, 26 % yield): MS m/e 443 $(M+H)^+$; ^1H NMR (DMSO-d_6 300 MHz) δ 1.37 (s 9H), 2.59 (m, 2H), 3.31 (m, 3H), 3.40 (m, 1H), 3.85 (m, 1H), 3.97 (d, 2H), 4.82 (s, 2H), 4.94 (d, 1H), 6.43 (d, 2H), 6.77 (d, 2H), 6.82 (m, 3H), 10.55 (s, 1H), 10.61 (s, 1H).

Step e) *tert*-Butyl 4-[(2,4-dioxo-1,3-thiazolidin-5-yl)amino]phenethyl{(2*R*)-2-hydroxy-3-[(2-oxo-2,3-dihydro-1*H*-benzimidazol-4-yl)oxy]propyl}carbamate

This compound was prepared from *tert*-butyl 4-aminophenethyl{(2*R*)-2-hydroxy-3-[(2-oxo-2,3-dihydro-1*H*-benzimidazol-4-yl)oxy]propyl}carbamate and 5-bromo-1,3-thiazolidine-2,4-dione in substantially the same manner as described in example 1, step d, and was obtained as a yellow solid (31 % yield): MS m/e 558 $(M+H)^+$; ^1H NMR (DMSO-d_6 300 MHz) δ 1.31 (s 9H), 2.64 (m, 2H), 3.41 (m, 5H), 3.84 (m, 1H), 3.96 (m, 2H), 4.92 (m, 1H),

6.45 (m, 1H), 6.56 (m, 3H), 6.81 (m, 2H), 6.97 (m, 2H), 10.55 (s, 1H), 10.59 (s, 1H), 12.25 (br, 1H).

Step f) 5-{4-[2-({(2*R*)-2-Hydroxy-3-[(2-oxo-2,3-dihydro-1*H*-benzimidazol-4-yl)oxy]-propyl}amino)ethyl]anilino}-1,3-thiazolidine-2,4-dione

This compound was prepared from *tert*-butyl 4-[(2,4-dioxo-1,3-thiazolidin-5-yl)amino]phenethyl{(2*R*)-2-hydroxy-3-[(2-oxo-2,3-dihydro-1*H*-benzimidazol-4-yl)oxy]propyl}carbamate and trifluoroacetic acid in substantially the same manner as described in example 1, step e, and was obtained as a light yellow solid (38 %yield): mp 172 ^{0}C; MS m/e 458 $(M+H)^+$; ^{1}H NMR (DMSO-d_6 300 MHz) δ 2.90 (m, 2H), 3.22 (m, 4H), 3.98 (m, 1H), 4.05 (m, 1H), 4.06 (m, 1H), 5.74 (d, 1H), 6.50 (d, 1H), 6.60 (m, 4H), 6.86 (t, 1H), 7.10 (m, 3H), 8.56 (s, 2H), 10.60 (s, 1H), 10.63 (s, 1H),12.19 (s, 1H);

Analysis for $C_{21}H_{23}N_5O_5S$ x 1 CF_3COOH Calc'd: C, 48.34; H, 4.23; N, 12.25

Found: C, 47.79; H, 4.48; N, 11.20.

Example 20

5-{[2-({[(2*R*)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino}methyl)-1-benzofuran-5-yl]amino}-1,3-thiazolidine-2,4-dione

Step a) 2-(Bromomethyl)-6-nitro-1-benzofuran

Acetoxime (50 g, 355 mmol) was added portionwise into a mixture of sodium hydride (60% in mineral oil, 15.52 g, 390.5 mmol) and N,N-dimethylformamide. The mixture was stirred for 1 hour. During this period the mixture was allowed to come to room temperature. The mixture was cooled to 0 ^{0}C, and 4-fluoro-nitrobenzene 92702 g, 372.7 mmol) was added slowly. The new mixture was stirred at 0 ^{0}C for 2 hours and then was stirred at room temperature for 16 hours. The reaction mixture was quenched with brine and the precipitated solid filtered and dried to give an off-white solid (66 g). this product was taken in ethanol (1000 mL) and anhydrous hydrochloric acid was passed through the mixture for 2 hours. The mixture was then refluxed for 20 hours and the volatiles were removed in vacuo. The residue was taken in water and the precipitated solid filtered and dried to give an off-white solid (50.6 g). this product was taken in carbon tetrachloride and 1,3-dibromo-5,5-dimethylhydantoin (40.4 g, 141.2 mmol) and benzoyl peroxide were added into the mixture. The mixture was then refluxed under UV light for 6 hours. The volatiles were removed in vacuo and the residue was taken in ethyl acetate and washed with water and brine. The organic extracts were dried over $MgSO_4$. Evaporation and

crystallization form ethyl ether/hexanes gave a white solid (59.6 g): ^{1}H NMR (DMSO-d_6 300 MHz) δ 5.0 (s, 2H), 7.24 (s, 1H), 7.83 (m, 1H), 8.24 (m, 1H), 8.63 (m, 1H).

Step b) (6-Nitro-1-benzofuran-2-yl)methanamine

A mixture of 2-(bromomethyl)-6-nitro-1-benzofuran (44.0 g, 171.9 mmol), potassium phthalimide (47.7 mmol), acetonitrile (1000 mL), and 18-C-6 (4.5 g, 17.19 mmol) was stirred at room temperature for 10 hours. The volatiles were removed in vacuo, and the residue was taken in ethyl acetate and washed with water. The organic extracts were dried over $MgSO_4$. Evaporation and crystallization form ethyl ether/hexanes gave an off-white solid (53.2 g).

This product was taken in ethanol and hydrazine (7.2 mL, 233 mmol) was added. The mixture was refluxed for 5 hours and the volatiles were removed in vacuo. The residue was acidified with hydrochloric acid, and the precipitated solids were filtered off and discarded. The filtrate was basified with sodium hydroxide (10 N) and extracted with ethyl acetate. The organic extracts were dried over $MgSO_4$. Evaporation and crystallization form ethyl ether/hexanes gave a brownish solid (24.6 g): MS m/e 192 M^+;

Analysis for $C_9H_8N_2O_3$ Calc'd: C, 56.25; H, 4.20; N, 14.58

Found: C, 56.21; H, 4.13; N, 14.41.

Step c) (1*R*)-1-(3-chlorophenyl)-2-{[(5-nitro-1-benzofuran-2-yl)methyl]amino}-1-ethanol

This compound was prepared from (*R*)-(+)-3-chlorostyrene oxide and (6-nitro-1-benzofuran-2-yl)methanamine as described in example 1, step b, to give a yellow solid (67 % yield), MS m/e 347 $(M+H)^+$; Analysis for $C_{17}H_{15}ClN_2O_4$ Calc'd: C, 58.88; H, 4.36; N, 8.08 Found: C, 58.75; H, 4.36; N, 8.01

Step d) *tert*-Butyl (2*R*)-2-(3-chlorophenyl)-2-hydroxyethyl[(5-nitro-1-benzofuran-2-yl)methyl]carbamate

This compound was prepared from (1*R*)-1-(3-chlorophenyl)-2-{[(5-nitro-1-benzofuran-2-yl)methyl]amino}-1-ethanol and di-tert-butyl dicarbonate as described in example 1, step c, to give a tan solid (91 % yield), MS m/e 447 $(M+H)^+$.

Step e) *tert*-Butyl (5-amino-1-benzofuran-2-yl)methyl[(2*R*)-2-(3-chlorophenyl)-2-hydroxyethyl]carbamate

A solution of *tert*-butyl (2*R*)-2-(3-chlorophenyl)-2-hydroxyethyl[(5-nitro-1-benzofuran-2-yl)-methyl]carbamate (2.95 g, 6.60 mmol) in methyl alcohol (30 mL) was added over 10 minutes into a slurry of iron (1.76 g, 33 mmol) and 0.025 M aqueous ammonium chloride

(33 mL). The reaction mixture was warmed up at reflux for 4 hours. The mixture was then filtered through celite and washed with hot methyl alcohol. The volatiles were removed in vacuo and the residue was neutralized with saturated aqueous bicarbonate, and extracted with dichloromethane. The organic extracts were dried over $MgSO_4$. Evaporation and purification by recrystallization from dichloromethane and hexanes gave a tan solid (1.80 g, 65 % yield): MS m/e 417 $(M+H)^+$; ^1H NMR (DMSO-d_6 300 MHz) δ 1.34 (s 9H), 3.27 (m, 1H), 3.45 (m, 1H), 4.57 (m, 2H), 4.82 (m, 3H), 5.69 (m, 1H), 6.52 (m, 2H), 6.66 (s, 1H), 7.18 (t, 1H), 7.31 (m, 4H).

Step f) *tert*-Butyl (2*R*)-2-(3-chlorophenyl)-2-hydroxyethyl({5-[(2,4-dioxo-1,3-thiazolidin-5-yl)amino]-1-benzofuran-2-yl}methyl)carbamate

This compound was prepared from *tert*-butyl (5-amino-1-benzofuran-2-yl)methyl[(2*R*)-2-(3-chlorophenyl)-2-hydroxyethyl]carbamate and 5-bromo-1,3-thiazolidine-2,4-dione in substantially the same manner as described in example 1, step d, and was obtained as a yellow solid (75 % yield), MS m/e 530 $(M-H)^+$; ^1H NMR (DMSO-d_6 300 MHz) δ 1.28 (s 9H), 3.24 (m, 1H), 3.40 (m, 1H), 4.54 (m, 2H), 4.81 (br, 1H), 5.66 (br, 1H), 6.47 (m, 1H), 6.61 (d, 1H), 6.65 (d, 1H), 6.78 (s, 1H), 6.96 (d, 1H), 7.28 (m, 5H), 12.16 (s, 1H).

Step g) 5-{[2-({[(2*R*)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino}methyl)-1-benzofuran-5-yl]amino}-1,3-thiazolidine-2,4-dione

This compound was prepared from *tert*-butyl (2*R*)-2-(3-chlorophenyl)-2-hydroxyethyl({5-[(2,4-dioxo-1,3-thiazolidin-5-yl)amino]-1-benzofuran-2-yl}methyl)carbamate and trifluoroacetic acid in substantially the same manner as described in example 1, step e, and was obtained as a light yellow solid (60 %yield): mp 70 ^0C; MS m/e 458 $(M+H)^+$; ^1H NMR (DMSO-d_6 300 MHz) δ 3.08 (m, 1H), 3.20 (m, 1H), 4.42 (m, 2H), 4.94 (d, 1H), 6.28 (d, 1H), 6.50 (d, 1H), 6.78 (d, 1H), 6.86 (s, 1H), 6.97 (s, 1H), 7.05 (d, 1H), 7.34 (m, 5H), 9.38 (br, 2H), 11.55 (br, 1H);

Analysis for $C_{20}H_{18}ClN_3O_4S$ x 1 CF_3COOH x 0.28 H_2O Calc'd: C, 47.90; H, 3.44; N, 7.62 Found: C, 46.84; H, 3.46; N, 7.12.

Example 21

5-(4-{2-[(2S)-2-Hydroxy-3-(naphthalen-2-yloxy)-propylamino]-ethyl}-phenylamino)-thiazolidine-2,4-dione

Step a) 2-[(2-Naphthyloxy)methyl]oxirane

NaH (60% in mineral oil, 2.16 g, 54.0 mmol) was added portionwise to 50 mL of DMF with stirring at room temperature under a nitrogen atmosphere. A solution of 2-naphthol (6.74 g, 46.28 mmol) in DMF (50 mL) was then added dropwise to this suspension over a period of 0.5 hour. After stirring for 1 hour a solution of (2*S*)-oxiranylmethyl 3-nitrobenzenesulfonate (10 g, 38.57 mmol) in DMF (50 mL) was added dropwise into this mixture over a period of 15 min. The mixture was then stirred at room temperature overnight. The reaction was quenched with aqueous ammonium chloride to pH 5 and further diluted with water. The formed solid was isolated by filtration to give (6.14 g, 80% yield): mp: 72-73 °C; MS m/z 200 M^+; Analysis for $C_{13}H_{12}O_2$ Calc'd: C, 77.98; H, 6.04; N, 0.00; Found: C, 78.12; H, 6.63; N, 0.12.

Step b) (2*S*)-1-[(4-Aminophenethyl)amino]-3-(2-naphthyloxy)-2-propanol

A mixture of 2-[(2-naphthyloxy)methyl]oxirane (3.0 g, 15.0 mmol), and 2-(4-aminophenyl)-ethylamine (6.1 mL, 45.0 mmol) in THF (20 mL) was stirred at room temperature under a nitrogen atmosphere overnight. The solvent was removed in vacuo and the residue was stirred in ethyl ether (4 X 150 mL) overnight. The solid was isolated by filtration to give an off-white solid (2.9 g, 58% yield): mp: 112-113 °C; MS m/z 336 M^+; Analysis for $C_{21}H_{24}N_2O_2$ Calc'd: C, 74.97; H, 7.19; N, 8.33; Found: C, 75.16; H, 7.18; N, 8.48.

Step c) 5-(4-{2-[(2S)-2-Hydroxy-3-(naphthalen-2-yloxy)-propylamino]-ethyl}-phenyl-amino)-thiazolidine-2,4-dione

A mixture of **(2*S*)-1-[(4-aminophenethyl)amino]-3-(2-naphthyloxy)-2-propanol** (2.86 g, 8.5 mmol), N,N-diisopropylethylamine (3.7 mL, 21.2 mmol) and di-tert-butyl dicarbonate (2.25 g, 10.2 mmol) in THF (55 mL) was stirred at room temperature under a nitrogen atmosphere for 3 hours. The reaction was quenched with saturated aqueous sodium bicarbonate and further diluted with water. The aqueous layer was extracted with ethyl acetate. The extract was washed with water, and dried with $MgSO_4$. Concentration and purification by flash column chromatography (hexanes/ethyl acetate 1/1) gave a white solid (2.34 g, 63% yield). A mixture of this product (2.3 g, 5.27 mmol), triethylamine (0.96 mL, 6.85 mmol) and 5-bromo-1,3-thiazolidine-2,4-dione (1.34 g, 6.85 mmol) in DMF (20

mL) was stirred at room temperature under a nitrogen atmosphere for 7 hours. The mixture was diluted with water and extracted with methylene chloride. The extract was washed with water, and dried with $MgSO_4$. Evaporation and purification by flash column chromatography (methylene chloride/methanol 95/5) gave a solid (2.15 g, 70% yield). A solution of this product (2.1 g, 3.8 mmol), trifluoroacetic acid (14 mL) and methylene chloride (20 mL) was stirred at room temperature under a nitrogen atmosphere for 30 min. The reaction mixture was concentrated to give an off-white solid (1.88 g, 77% yield): mp: 90-91 °C; MS m/z 452 $(M+H)^+$; Analysis for $C_{24}H_{25}N_3O_4S$ x 1.3 H_2O x 1.0 $CF3CO_2H$ Calc'd: C, 53.02; H, 4.89; N, 7.13; Found: C, 53.28; H, 4.41; N, 6.88.

Example 22

5-(4-{2-[(2S)-3-(Biphenyl-4-yloxy)-2-hydroxy-propylamino]-ethyl}-phenylamino)-thiazolidine-2,4-dione

Step a) 2-[([1,1'-Biphenyl]-4-yloxy)methyl]oxirane

The title compound was prepared from 4-phenylphenol and (2*S*)-oxiranylmethyl 3-nitro-benzenesulfonate in substantially the same manner as described in example 21, step a. The product was obtained as a white solid: mp: 91-92 °C; MS m/z 226 M^+; Analysis for $C_{15}H_{14}O_2$ Calc'd: C, 79.62; H, 6.24; N, 0.00; Found: C, 79.35; H, 6.36; N, -0.03.

Step b) (2*S*)-1-[(4-Aminophenethyl)amino]-3-([1,1'-biphenyl]-4-yloxy)-2-propanol

The title compound was prepared from 2-[([1,1'-biphenyl]-4-yloxy)methyl]oxirane, and 2-(4-aminophenyl)ethylamine in substantially the same manner, as described in example 21, step b. The product was obtained as a white solid: 118-119 °C; MS m/z 362 M^+; Analysis for $C_{23}H_{26}N_2O_2$ Calc'd: C, 76.21; H, 7.23; N, 7.73;
Found: C, 75.83; H, 7.24; N, 7.58.

Step c) 5-(4-{2-[(2S)-3-(Biphenyl-4-yloxy)-2-hydroxy-propylamino]ethyl}phenyl-amino)thiazolidine-2,4-dione

The title compound was prepared from (2*S*)-1-[(4-aminophenethyl)amino]-3-([1,1'-biphenyl]-4-yloxy)-2-propanol, and 5-bromo-1,3-thiazolidine-2,4-dione in substantially the same manner, as described in example 21, step c. The product was obtained as a white solid: mp: 70-71 °C; MS m/z 478 $(M+H)^+$; Analysis for $C_{26}H_{27}N_3O_4S$ x 0.36 DMF x 2.0 F_3CCO_2H Calc'd: C, 49.54; H, 4.54; N, 6.25; Found: C, 49.56; H, 4.27; N, 6.22.

Example 23

5-(4-{2-[2-Hydroxy-3-(naphthalen-1-yloxy)-propylamino]-ethyl}-phenylamin)-thiazolidine-2,4-dione

Step a) 2-[(1-Naphthyloxy)methyl]oxirane

The title compound was prepared from 1-naphthol and (2*S*)-oxiranylmethyl 3-nitrobenzenesulfonate in substantially the same manner as described in example 21, step a. The product was obtained as an oil: MS m/z 200 M^+.

Step b) (2*S*)-1-[(4-Aminophenethyl)amino]-3-(1-naphthyloxy)-2-propanol

The title compound was prepared from 2-[(1-naphthyloxy)methyl]oxirane, and 2-(4-aminophenyl)ethylamine in substantially the same manner, as described in example 21, step b. The product was obtained as a light yellow sticky solid: 107-108 °C; MS m/z 337 $(M+H)^+$; Analysis for $C_{21}H_{24}N_2O_2$ Calc'd: C, 74.97; H, 7.19; N, 8.33;
Found: C, 74.56; H, 7.36; N, 8.49.

Step c) 5-(4-{2-[2-Hydroxy-3-(naphthalen-1-yloxy)-propylamino]-ethyl}phenylamino)-thiazolidine-2,4-dione

The title compound was prepared from (2*S*)-1-[(4-aminophenethyl)amino]-3-(1-naphthyloxy)-2-propanol, and 5-bromo-1,3-thiazolidine-2,4-dione in substantially the same manner, as described in example 21, step c. The product was obtained as an off-white solid: mp: 61-62 °C; MS m/z 452 $(M+H)^+$; Analysis for $C_{23}H_{27}N_4O_4S$ Na x 1.6 H_2O x 1.5 CF_3CO_2H Calc'd: C, 49.79; H, 4.60; N, 6.45; Found: C, 50.16; H, 4.22; N, 6.08.

Example 24

5-(4-{2-[(2S)-3-(Benzo[1,3]dioxol-5-yloxy)-2-hydroxy-propylamino]ethyl}phenylamino)-thiazolidine-2,4-dione

Step a) 5-(2-Oxiranylmethoxy)-1,3-benzodioxole

The title compound was prepared from 3,4-methylenedioxyphenol and (2*S*)-oxiranylmethyl 3-nitrobenzenesulfonate in substantially the same manner as described in example 21, step a. The product was obtained as an oil: MS m/z 124 M^+; Analysis for $C_{15}H_{14}O_2$ Calc'd: C, 61.85; H, 5.19; N, 0.00; Found: C, 61.53; H, 5.22; N, 0.14.

Step b) (2*S*)-1-[(4-Aminophenethyl)amino]-3-(1,3-benzodioxol-5-yloxy)-2-propan l

The title compound was prepared from 5-(2-oxiranylmethoxy)-1,3-benzodioxole and 2-(4-aminophenyl)ethylamine in substantially the same manner, as described in example 21,

step b. The product was obtained as a solid: 96-97 °C; MS m/z 331 $(M+H)^+$; Analysis for $C_{18}H_{22}N_2O_4$ Calc'd: C, 65.44; H, 6.71; N, 8.48; Found: C, 65.26; H, 6.63; N, 8.52.

Step c) 5-(4-{2-[(2S)-3-(Benzo[1,3]dioxol-5-yloxy)-2-hydroxy-propylamino]ethyl}-phenylamino)-thiazolidine-2,4-dione

The title compound was prepared from (2*S*)-1-[(4-aminophenethyl)amino]-3-(1,3-benzodioxol-5-yloxy)-2-propanol, and 5-bromo-1,3-thiazolidine-2,4-dione in substantially the same manner, as described in example 21, step c. The product was obtained as an off-white solid: mp: 65 °C (decomposed); MS m/z 446 $(M+H)^+$; Analysis for $C_{21}H_{23}N_3O_6S$ x 0.87 H_2O x 1.0 CF_3CO_2H Calc'd: C, 48.31; H, 4.66; N, 7.19;
Found: C, 48.51; H, 4.49; N, 7.08.

Example 25

5-[(4-{2-[(2S)-3-(4-Benzyloxy-phenoxy)-2-hydroxy-propylamino]-ethyl}-phenyl)-(4-bromo-benzyl)-amino]-thiazolidine-2,4-dione

Step a) *tert*-Butyl (2*S*)-3-[4-(benzyloxy)phenoxy]-2-hydroxypropyl{4-[(4-bromo-benzyl)amino]phenethyl}carbamate

A mixture of *tert*-butyl 4-aminophenethyl{(2*S*)-3-[4-(benzyloxy)phenoxy]-2-hydroxypropyl}-carbamate (0.20 g, 0.41 mmol), 4-bromobenzyl bromide (0.16 g, 0.62 mmol) and potassium carbonate (0.08 g, 0.62 mmol) in acetone (2.2 mL) was stirred at room temperature for two days. The mixture was diluted with water and extracted with ethyl acetate. The extract was washed with water and dried with $MgSO_4$. Evaporation and purification by flash column chromatography (hexane/ethyl acetate 7/3) gave a white solid (0.06 g, 21%): MS m/z 661 $[M+H]^+$.

Step b) 5-[(4-{2-[(2S)-3-(4-Benzyloxy-phenoxy)-2-hydroxy-propylamino]ethyl}-phenyl)-(4-bromo-benzyl)-amino]-thiazolidine-2,4-dione

The title compound was prepared from *tert*-butyl (2*S*)-3-[4-(benzyloxy)phenoxy]-2-hydroxypropyl{4-[(4-bromobenzyl)amino]phenethyl}carbamate, and 5-bromo-1,3-thiazolidine-2,4-dione in substantially the same manner, as described in example 4. The product was obtained as a light yellow solid: mp: 50-52 °C; MS m/z 676 $[M+H]^+$; Analysis for $C_{34}H_{34}BrN_3O_5S$ x 1.6 CF_3CO_2H Calc'd: C, 52.01; H, 4.18; N, 4.89;
Found: C, 51.73; H, 4.27; N, 4.57.

Example 26

5-[(4-{2-[(2S)-3-(4-Benzyloxy-phenoxy)-2-hydroxy-propylamino]ethyl}phenyl)methyl-amino]-thiazolidine-2,4-dione

Step a) *tert*-Butyl (2*S*)-3-[4-(benzyloxy)phenoxy]-2-hydroxypropyl[4-(methylamino) phenethyl]carbamate

The title compound was prepared from *tert*-butyl 4-aminophenethyl{(2*S*)-3-[4-(benzyloxy)-phenoxy]-2-hydroxypropyl}carbamate and iodomethane in substantially the same manner, as described in example 25, step a. The product was obtained as an oil. MS m/z 507 $[M+H]^+$.

Step b) 5-[(4-{2-[(2S)-3-(4-Benzyloxy-phenoxy)-2-hydroxy-propylamino]ethyl}-phenyl)methyl-amino]-thiazolidine-2,4-dione

The title compound was prepared from *tert*-butyl (2*S*)-3-[4-(benzyloxy)phenoxy]-2-hydroxypropyl[4-(methylamino)phenethyl]carbamate, and 5-bromo-1,3-thiazolidine-2,4-dione in substantially the same manner, as described in example 4. The product was obtained as an off-white solid; mp: 51-53 °C; MS m/z 522 $(M+H)^+$; Analysis for $C_{28}H_{31}N_3O_5S$ x 1.0 CF_3CO_2H Calc'd: C, 56.69; H, 5.07; N, 6.61;
Found: C, 57.66; H, 4.57; N, 6.10.

Example 27

5-[(4-{2-[(2S)-3-(4-Benzyloxy-phenoxy)-2-hydroxy-propylamino]-ethyl}- phenyl)-[3-(4-fluoro-phenyl)-prop-2-ynyl]-amino}-thiazolidine-2,4-dione

Step a) *tert*-Butyl (2*S*)-3-[4-(benzyloxy)phenoxy]-2-hydroxypropyl(4-{[3-(4-fluoro-phenyl)-2-propynyl]amino}phenethyl)carbamate

The title compound was prepared from *tert*-butyl 4-aminophenethyl{(2*S*)-3-[4-(benzyloxyphenoxy]-2-hydroxypropyl}carbamate, and 1-(3-bromo-1-propynyl)-4-fluorobenzene (US patent no. 5,574,051) in substantially the same manner, as described in example 25, step a. The product was obtained as a semi-solid: MS m/z 625 $[M+H]^+$.

Step b) 5-[(4-{2-[(2S)-3-(4-Benzyloxy-phenoxy)-2-hydroxypropylamino]ethyl}phenyl)-[3-(4-fluoro-phenyl)-prop-2-ynyl]-amino}-thiazolidine-2,4-dione

The title compound was prepared from *tert*-butyl (2*S*)-3-[4-(benzyloxy)phenoxy]-2-hydroxypropyl(4-{[3-(4-fluorophenyl)-2-propynyl]amino}phenethyl)carbamate, and 5-bromo-1,3-thiazolidine-2,4-dione in substantially the same manner, as described in

example 4. The product was obtained as an off-white solid: mp: 99-101 °C; MS m/z 640 $(M+H)^+$; Analysis for $C_{36}H_{34}FN_3O_5S$ x 0.27 H_2O x 0.24 CF_3CO_2H Calc'd: C, 65.21; H, 5.22; N, 6.25; Found: C, 65.52; H, 5.25; N, 6.16.

Example 28

5-[(4-Bromo-benzyl)-(4-{2-[(2S)-2-hydroxy-3-(4-hydroxy-phenoxy)-propylamino]-ethyl}-phenyl)-amino]-thiazolidine-2,4-dione

Step a) *tert*-Butyl 4-aminophenethyl[(2*S*)-2-hydroxy-3-(4-hydroxyphenoxy)propyl]-carbamate

A mixture of *tert*-butyl 4-aminophenethyl{(2*S*)-3-[4-(benzyloxy)phenoxy]-2-hydroxypropyl}-carbamate (0.54 g, 1.1 mmol), and 10 % Pd-C (0.05 g) in ethanol (30 mL) was hydrogenated at room temperature at 50 psi for 5.5 hours. Filtration and evaporation yielded an oil. MS m/z 401 $(M-H)^-$.

Step b) *tert*-Butyl 4-[(4-bromobenzyl)amino]phenethyl[(2*S*)-2-hydroxy-3-(4-hydroxy-phenoxy)propyl]carbamate

The title compound was prepared from *tert*-butyl 4-aminophenethyl[(2*S*)-2-hydroxy-3-(4-hydroxyphenoxy)propyl]carbamate and iodomethane in substantially the same manner, as described in example 4. The product was obtained as a white solid: MS m/z 571 $[M+H]^+$.

Step c) 5-[(4-Bromo-benzyl)-(4-{2-[(2S)-2-hydroxy-3-(4-hydroxy-phenoxy)-propyl-amino]-ethyl}-phenyl)-amino]-thiazolidine-2,4-dione

The title compound was prepared from *tert*-butyl 4-[(4-bromobenzyl)amino]phenethyl[(2*S*)-2-hydroxy-3-(4-hydroxyphenoxy)propyl]carbamate, and 5-bromo-1,3-thiazolidine-2,4-dione in substantially the same manner, as described in example 4. The product was obtained as an off-white solid: mp: 79 °C (decomposed); MS m/z 584 $(M-H)^-$; Analysis for $C_{27}H_{28}BrN_3O_5S$ x 0.59 H_2O x 1.0 CF_3CO_2H Calc'd: C, 48.98; H, 4.28; N, 5.91; Found: C, 48.77; H, 4.32; N, 5.54.

Example 29

5-((4-Bromo-benzyl)-{4-[2-((2S)-2-hydroxy-3-phenoxy-propylamino)- ethyl]-phenyl}-amino)-thiazolidine-2,4-dione

Step a) *tert*-Butyl 4-[(4-bromobenzyl)amino]phenethyl[(2*S*)-2-hydroxy-3-phenoxy-propyl]carbamate

A mixture of (2*S*)-1-[(4-aminophenethyl)amino]-3-phenoxy-2-propanol (0.503 g, 1.76 mmol), N,N-diisopropylethylamine (0.765 mL, 4.4 mmol) and di-tert-butyl dicarbonate (0.461 g, 2.11 mmol) in THF (11 mL) was stirred at room temperature under a nitrogen atmosphere for 3 hours. The reaction was quenched with saturated aqueous sodium bicarbonate and further diluted with water. The aqueous layer was extracted with ethyl acetate. The extract was washed with water, dried with $MgSO_4$ and concentrated to give a light brown solid (0.45 g, 66%). A mixture of this product (0.44 g, 1.14 mmol), 4-bromobenzyl bromide (0.58 g, 2.28 mmol) and potassium carbonate (0.31 g, 2.28 mmol) in acetone (6 mL) was stirred at room temperature for 6 hours. The mixture was diluted with water and extracted with ethyl acetate. The extract was washed with water and dried with $MgSO_4$. Evaporation and purification by flash column chromatography (hexane/ethyl acetate 7/3) gave an oil (0.33 g, 53%): mp: °C; MS m/z 555 $[M+H]^+$.

Step b) 5-((4-Bromo-benzyl)-{4-[2-((2S)-2-hydroxy-3-phenoxy-propylamino)-ethyl]-phenyl}-amino)-thiazolidine-2,4-dione

The title compound was prepared from *tert*-butyl 4-[(4-bromobenzyl)amino]phenethyl-[(2*S*)-2-hydroxy-3-phenoxypropyl]carbamate, and 5-bromo-1,3-thiazolidine-2,4-dione in substantially the same manner, as described in example 4. The product was obtained as an off-white solid: mp: 52-54 °C; MS m/z 570 $(M+H)^+$; Analysis for $C_{27}H_{28}BrN_3O_4S$ x 0.6 H_2O x 1.5 CF_3CO_2H Calc'd: C, 47.89; H, 4.11; N, 5.59; Found: C, 47.54; H, 4.08; N, 5.22.

Example 30

5-{4-[2-((2S)-2-Hydroxy-2-pyridin-3-yl-ethylamino)-ethyl]-phenylamino}-thiazolidine-2,4-dione

Step a) 3-[(2*S*)-Oxiranyl]pyridine

A solution of borane-THF (1M solution, 15 mL) was added dropwise to a 0 °C, stirred solution of (S)-2-methyl-CBS-oxazaborolidine monohydrate (0.738 g, 2.5 mmol) in THF (10 mL) over a period of 10 min. After stirred at 0 °C for 10 minutes the mixture was then added dropwise into a cold (0 °C) stirred suspension of 3-(2-bromoacetyl)pyridine

hydrobromide (7.0 g, 24.9 mmol) in THF (50 mL) over a period of 10 minutes. After addition was completed the mixture was stirred at room temperature under a nitrogen atmosphere overnight. The reaction was cooled to 0 °C and quenched with dry HCl (0.5 M in methanol, 9 mL) The mixture was further diluted with water and extracted with ethyl acetate. The extract was washed with water and dried with $MgSO_4$. Evaporation and purification by flash column chromatography (methylene chloride/methanol 95/5) gave (1*R*)-2-bromo-1-(3-pyridinyl)-1-ethanol as a brown oil (1.72 g, 34%). This solid (1.71 g, 8.5 mmol) was dissolved in THF (15 mL) and 5 N aqueous sodium hydroxide (30 mL) was added. After the solution was stirred at room temperature for 10 minutes, the mixture was diluted with water and extracted with methylene chloride. The extract was washed with water, dried with $MgSO_4$, and concentrated to give a white solid (0.72 g, 72%): MS m/z 122 $(M+H)^+$.

Step b) (1*S*)-2-[(4-Aminophenethyl)amino]-1-(3-pyridinyl)-1-ethanol

The title compound was prepared from 3-[(2*S*)-oxiranyl]pyridine, and 2-(4-aminophenyl)-ethylamine in substantially the same manner, as described in example 21, step b. The product was obtained as an off-white solid: 82-83 °C; MS m/z 258 $(M+H)^+$.

Step c) 5-{4-[2-((2S)-2-Hydroxy-2-pyridin-3-yl-ethylamino)-ethyl]-phenylamino}-thiazolidine-2,4-dione

The title compound was prepared from (1*S*)-2-[(4-aminophenethyl)amino]-1-(3-pyridinyl)-1-ethanol, and 5-bromo-1,3-thiazolidine-2,4-dione in substantially the same manner, as described in example 21, step c. The product was obtained as a yellow solid: mp: 46-48°C; MS m/z 373 $(M+H)^+$; Analysis for $C_{18}H_{20}N_4O_3S$ x 1.5 H_2O x 2.5 CF_3CO_2H x 0.1 C_2H_5O Calc'd: C, 40.62; H, 3.86; N, 8.09; Found: C, 40.87; H, 3.67; N, 7.78.

Example 31

5-{4-[2-((2R)-2-Hydroxy-2-pyridin-3-yl-ethylamino)-ethyl]-phenylamino}- thiazolidine-2,4-dione

Step a) 3-[(2*R*)-Oxiranyl]pyridine

The title compound was prepared from 3-(2-bromoacetyl)pyridine hydrobromide, and (*R*)-2-methyl-CBS-oxazaborolidine monohydrate in substantially the same manner, as described in example 30, step a. The product was obtained as an oil. MS m/z 121 M^+.

Step b) (1*R*)-2-[(4-Aminophenethyl)amino]-1-(3-pyridinyl)-1-ethanol

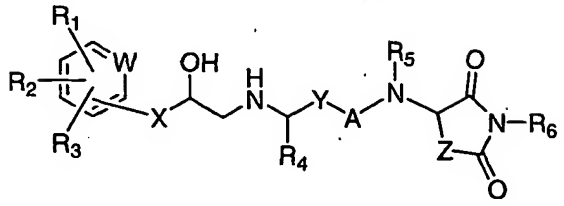
The title compound was prepared from 3-[(2*R*)-oxiranyl]pyridine, and 2-(4-aminophenyl)-ethylamine in substantially the same manner, as described in example 30, step b. The product was obtained as a light brown solid: MS m/z 258 $(M+H)^+$.

Step c) 5-{4-[2-((2R)-2-Hydroxy-2-pyridin-3-yl-ethylamino)-ethyl]-phenylamino}-thiazolidine-2,4-dione

The title compound was prepared from (1*R*)-2-[(4-aminophenethyl)amino]-1-(3-pyridinyl)-1-ethanol, and 5-bromo-1,3-thiazolidine-2,4-dione in substantially the same manner, as described in example 30, step c. The product was obtained as a yellow solid: mp: 65-67°C; MS m/z 373 $(M+H)^+$; Analysis for $C_{18}H_{20}N_4O_3S$ x 1.26 H_2O x 2.2 CF_3CO_2H Calc'd: C, 41.65; H, 3.86; N, 8.67; Found: C, 41.86; H, 3.81; N, 8.24.

CLAIMS

1. A compound of formula I having the structure



I

wherein,

R_1, R_2, R_3 are each, independently, hydrogen, alkyl of 1-6 carbon atoms, aryl of 6 to 10 carbon atoms, aryloxy of 6-10 carbon atoms, halogen, trifluoromethyl of 1-6 carbon atoms, arylalkoxy of 7-14 carbon atoms, arylalkyl of 7-14 carbon atoms, alkoxy of 1-6 carbon atoms, hydroxy, nitro, amino, aminocarbonyl, alkylamino of 1-6 carbon atoms, dialkyl amino of 1-6 carbon atoms per alkyl group, formamido, ureido, acyl of 2-7 carbon atoms, acylamino of 2-7 carbon atoms, amino, alkylsulfonylamino of 1-6 carbon atoms, or arylsulfonylamino of 6 to 10 carbon atoms; or two of R_1, R_2, and R_3 are taken together to form a phenyl ring or a heterocyclic ring which is fused to the ring which contains the R_1, R_2, or R_3 substituents, wherein the heterocyclic ring contains 1-3 heteroatoms selected from N, O, or S;

R_4 is hydrogen or alkyl of 1-6 carbon atoms;

R_5 is hydrogen, alkyl of 1-6 carbon atoms, aryl of 6-10 carbon atoms, arylalkyl of 7-14 carbon atoms, halogen substituted arylalkyl of 7-14 carbon atoms, arylalkene of 8-16 carbon atoms, arylalkyne of 8-16 carbon atoms, alkoxycarbonyl of 2-7 carbon atoms, aryloxycarbonyl of 7-11 carbon atoms, alkylsulfonyl of 1-6 carbon atoms, arylsulfonyl of 1-6 carbon atoms, halogen substituted arylalkene of 8-16 carbon atoms, or halogen substituted arylalkyne of 8-16 carbon atoms;

R_6 is hydrogen, alkyl of 1-6 carbon atoms, aryl or arylalkyl of 7-14 carbon atoms;

A is phenyl, naphthyl, benzofuryl, or benzothienyl;

X is bond, $-OCH_2-$, or $-SCH_2-$;

Y is alkyl of 1-6 carbon atoms, or alkoxy of 1-6 carbon atoms or a bond;

Z is carbon, sulfur, oxygen, or nitrogen;

W is carbon or nitrogen;

or a pharmaceutically acceptable salt thereof.

2. A compound according to Claim 1 wherein

R_1, R_2, R_3 are each, independently, hydrogen, alkyl of 1-6 carbon atoms, aryl of 6 to 10 carbon atoms, aryloxy of 6-10 carbon atoms, halogen, arylalkoxy of 7-14 carbon atoms, arylalkyl of 7-14 carbon atoms, alkoxy of 1-6 carbon atoms, hydroxy, or alkylsulfonylamino of 1-6 carbon atoms; or two of R_1, R_2, and R_3 are taken together to form a heterocyclic ring which is fused to the ring which contains the R_1, R_2, or R_3 substituents, wherein the heterocyclic ring contains 1-3 heteroatoms selected from N, O, or S;

R_4 is hydrogen or alkyl of 1-6 carbon atoms;

R_5 is hydrogen, alkyl of 1-6 carbon atoms, halogen substituted arylalkyl of 7-14 carbon atoms, or halogen substituted arylalkyne of 8-16 carbon atoms;

R_6 is hydrogen, or alkyl of 1-6 carbon atoms;

A is phenyl, or benzofuryl;

X is bond, or $-OCH_2-$;

Y is alkyl of 1-6 carbon atoms or a bond;

Z is sulfur;

W is carbon or nitrogen;

or a pharmaceutically acceptable salt thereof.

3. A compound according to either Claim 1 or Claim 2 wherein X is $-OCH_2$.

4. A compound according to either Claim 1 or Claim 2 wherein X is a bond.

5. A compound according to any one of Claims 1-4 wherein A is phenyl.

6. A compound according to any one of Claims 1-5 wherein W is carbon.

7. A compound according to any one of Claims 1-5 wherein W is nitrogen.

8. A compound according to any one of Claims 1-7 wherein R_4 is hydrogen.

9. A compound according to any one of Claims 1-7 wherein R_4 is alkyl of 1-6 carbon atoms.

10. A compound according to any one of Claims 1-9 wherein R_5 is hydrogen.

11. A compound according to any one of Claims 1-9 wherein R_5 is alkyl of 1-6 carbon atoms.

12. A compound according to any one of Claims 1-11 wherein R_6 is hydrogen.

13. A compound according to any one of Claims 1-11 wherein R_6 is alkyl of 1-6 carbon atoms.

14. A compound according to any one of Claims 1-13 wherein Y is alkyl of 1-6 carbon atoms.

15. A compound according to Claim 1 which is

a) 5-[4-(2-{[(2*S*)-2-Hydroxy-3-(4-phenoxyphenoxy)propyl]amino}ethyl)anilino]-1,3-thiazolidine-2,4-dione;

b) 5-{4-[2-({(2*S*)-3-[4-(Benzyloxy)phenoxy]-2-hydroxypropyl}amino)ethyl]anilino}-3-methyl-1,3-thiazolidine-2,4-dione;

c) 5-[4-(2-{[(2*R*)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino}ethyl)anilino]-3-methyl-1,3-thiazolidine-2,4-dione;

d) 5-{4-[2-({(2*S*)-3-[4-(Benzyloxy)phenoxy]-2-hydroxypropyl}amino)ethyl]anilino}-1,3-thiazolidine-2,4-dione;

e) 5-[4-(2-{[(2*S*)-2-Hydroxy-3-(4-hydroxyphenoxy)propyl]amino}ethyl)anilino]-1,3-thiazolidine-2,4-dione;

f) 5-[4-(2-{[(2*R*)-2-(3-Chlorophenyl)-2-hydroxy-ethyl]amino}ethyl)anilino]-1,3-thiazolidine-2,4-dione;

g) 5-[4-(2-{[(2*R*)-2-Hydroxy-2-phenylethyl]amino}ethyl)anilino]-1,3-thiazolidine-2,4-dione;

h) 5-[4-(2-{[(2*S*)-3-(4-Fluorophenoxy)-2-hydroxypropyl]amino}ethyl)anilino]-1,3-thiazolidine-2,4-dione;

i) 5-[4-(2-{[(2*S*)-2-Hydroxy-3-phenoxypropyl]amino}ethyl)anilino]-1,3-thiazolidine-2,4-dione;

j) 5-[4-(2-{[(2*S*)-2-Hydroxy-3-(4-methoxyphenoxy)propyl]amino}ethyl)anilino]-1,3-thiazolidine-2,4-dione;

k) 5-{4-[2-({(2*S*)-3-[3-(Benzyloxy)phenoxy]-2-hydroxypropyl}amino)ethyl]anilino}-1,3-thiazolidine-2,4-dione;

l) 5-[4-(2-{[(2*S*)-2-Hydroxy-3-(3-hydroxyphenoxy)propyl]amino}ethyl)anilino]-1,3-thiazolidine-2,4-dione;

m) 5-[4-(2-{[(2*S*)-3-(9*H*-Carbazol-4-yloxy)-2-hydroxypropyl]amino}ethyl)anilino]-1,3-thiazolidine-2,4-dione;

n) *N*-{5-[(1*S*)-2-({4-[(2,4-Dioxo-1,3-thiazolidin-5-yl)amino]phenethyl}amino)-1-hydroxyethyl]-2-hydroxyphenyl}methanesulfonamide;

o) 5-[4-(2-{[(2*S*)-3-(1-Benzofuran-5-yloxy)-2-hydroxypropyl]amino}ethyl)anilino]-1,3-thiazolidine-2,4-dione;

p) 5-[4-(2-{[(2*S*)-3-(4-Butoxyphenoxy)-2-hydroxypropyl]amino}ethyl)anilino]-1,3-thiazolidine-2,4-dione;

q) 5-[4-(2-{[(2*S*)-2-Hydroxy-3-phenoxypropyl]amino}ethyl)(methyl)anilino]-1,3-thiazolidine-2,4-dione.;

r) 5-[4-(2-{[(2*R*)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino}propyl)anilino]-1,3-thiazolidine-2,4-dione;

s) 5-{4-[2-({(2*R*)-2-Hydroxy-3-[(2-oxo-2,3-dihydro-1*H*-benzimidazol-4-yl)oxy]propyl}-amino)ethyl]anilino}-1,3-thiazolidine-2,4-dione;

t) 5-{[2-({[(2*R*)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino}methyl)-1-benzofuran-5-yl]-amino}-1,3-thiazolidine-2,4-dione;

u) 5-(4-{2-[(2S)-2-Hydroxy-3-(naphthalen-2-yloxy)-propylamino]-ethyl}-phenylamino)-thiazolidine-2,4-dione;

v) 5-(4-{2-[(2S)-3-(Biphenyl-4-yloxy)-2-hydroxy-propylamino]-ethyl}- phenylamino)-thiazolidine-2,4-dione;

w) 5-(4-{2-[2-Hydroxy-3-(naphthalen-1-yloxy)-propylamino]-ethyl}- phenylamino)-thiazolidine-2,4-dione;

x) 5-(4-{2-[(2S)-3-(Benzo[1,3]dioxol-5-yloxy)-2-hydroxy-propylamino]ethyl}phenyl-amino)-thiazolidine-2,4-dione;

y) 5-(4-{2-[(2S)-3-(4-Benzyloxy-phenoxy)-2-hydroxy-propylamino]ethyl}phenylamino)-thiazolidine-2,4-dione;

z) 5-[(4-{2-[(2S)-3-(4-Benzyloxy-phenoxy)-2-hydroxy-propylamino]-ethyl}- phenyl)-(4-bromo-benzyl)-amino]-thiazolidine-2,4-dione;

aa) 5-[(4-{2-[(2S)-3-(4-Benzyloxy-phenoxy)-2-hydroxy-propylamino]ethyl}phenyl)-methylamino]-thiazolidine-2,4-dione;

bb) 5-[(4-{2-[(2S)-3-(4-Benzyloxy-phenoxy)-2-hydroxy-propylamino]-ethyl}-phenyl)-[3-(4-fluoro-phenyl)-prop-2-ynyl]-amino}-thiazolidine-2,4-dione;

cc) 5-[(4-Bromo-benzyl)-(4-{2-[(2S)-2-hydroxy-3-(4-hydroxy-phenoxy)-propylamino]-ethyl}-phenyl)-amino]-thiazolidine-2,4-dione;

dd) 5-((4-Bromo-benzyl)-{4-[2-((2S)-2-hydroxy-3-phenoxy-propylamino)-ethyl]-phenyl}-amino)-thiazolidine-2,4-dione;

ee) 5-{4-[2-((2S)-2-Hydroxy-2-pyridin-3-yl-ethylamino)-ethyl]-phenylamino}-thiazolidine-2,4-dione; or

ff) 5-{4-[2-((2R)-2-Hydroxy-2-pyridin-3-yl-ethylamino)-ethyl]-phenylamino}-thiazolidine-2,4-dione

or a pharmaceutically acceptable salt thereof.

16. A method of treating metabolic disorders mediated by insulin resistance or hyperglycemia in a mammal in need thereof which comprises providing to said mammal, an effective amount of a compound of formula I as defined in any one of Claims 1-15.

17. A method of treating or inhibiting type II diabetes in a mammal in need thereof which comprises providing to said mammal, an effective amount of a compound of Formula I as defined in any one of Claims 1-15.

18. A method of modulating glucose levels in a mammal in need thereof which comprises providing to said mammal, an effective amount of a compound of formula I as defined in any one of Claims 1-15.

19. A method of treating or inhibiting urinary incontinence in a mammal in need thereof which comprises providing to said mammal an effective amount of a compound of formula I as defined in any one of Claims 1-15.

20. A method of treating or inhibiting atherosclerosis, gastrointestinal disorders, neurogenetic inflammation, glaucoma, or ocular hypertension in a mammal in need thereof, which comprises providing to said mammal an effective amount of a compound of formula I as defined in any one of Claims 1-15.

21. A method of increasing the lean meat to fat ratio in a mammal in need thereof, which comprises providing to said mammal an effective amount of a compound of formula I as defined in any one of Claims 1-15.

22. Use of a compound of formula I as claimed in any one of Claims 1 to 15 or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for treating metabolic disorders mediated by insulin resistance or hyperglycemia in a mammal.

23. Use of a compound of formula I as claimed in any one of Claims 1 to 15 or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for treating or inhibiting type II diabetes in a mammal.

24. Use of a compound of formula I as claimed in any one of Claims 1 to 15 or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for modulating glucose levels in a mammal.

25. Use of a compound of formula I as claimed in any one of Claims 1 to 15 or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for treating or inhibiting urinary incontinence in a mammal.

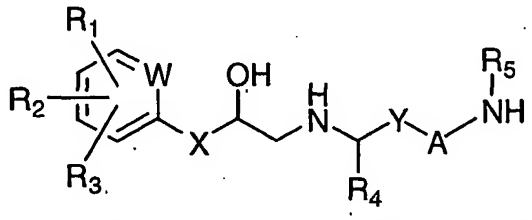
26. Use of a compound of formula I as claimed in any one of Claims 1 to 15 or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for treating or inhibiting atherosclerosis, gastrointestinal disorders, neurogenetic inflammation, glaucoma, or ocular hypertension in a mammal.

27. Use of a compound of formula I as claimed in any one of Claims 1 to 15 or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for increasing the lean meat to fat ratio in a mammal.

28. A pharmaceutical composition which comprises a compound of formula I as defined in any one of Claims 1-15 and a pharmaceutically acceptable carrier.

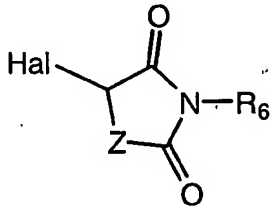
29. A process for preparing a compound of formula I as claimed in Claim 1 which comprises one of the following:

a) reacting a compound of formula II



II

wherein R_1, R_2, R_3, R_4, R_5, W, X, Y and A are as defined in Claim 1 with a compound of formula III



III

wherein Z and R_6 are as defined in Claim 1 and Hal is halogen, to give a compound of formula I;

or

b) removing any protecting groups from a compound of formula I in which at least one substituent carries a protecting group to give a compound of formula ;

or

c) converting a basic compound of formula I to a salt thereof by reaction with a pharmaceutically acceptable acid;

or

d) converting a compound of formula I having one or more reactive substituent groups to a different compound of formula I;

or

e) isolating an isomer of a compound of formula I from a mixture thereof.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 01/22408

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D277/42 C07D417/12 A61K31/426 A61K31/427 A61K31/4439 A61P3/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WEBER A E ET AL: "Potent, selective benzenesulfonamide agonists of the human beta3 adrenergic receptor" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 8, no. 9, 1 May 1998 (1998-05-01), pages 1101-1106, XP004137028 the whole document	1-29
A	BARRIE C C CANTELLO ET AL: "''Omega-(heterocyclylamino)alkoxy!benzyl! -2,4-thiazolidinediones as potent antihyperglycemic agents" JOURNAL OF MEDICINAL CHEMISTRY, vol. 37, no. 23, 1994, pages 3977-3985, XP002127022 the whole document	1,16-28

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 November 2001	28/11/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Allard, M

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 01/22408

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,Y	US 6 214 842 B1 (MALAMAS M S ET AL) 10 April 2001 (2001-04-10) the whole document	1-29
P,X	MALAMAS M S ET AL: "Potent, selective aminothiazolidinediones agonists of the human beta3 adrenergic receptor" MEDICINAL CHEMISTRY RESEARCH, vol. 10, no. 3, 2000, pages 164-177, XP001031326 the whole document	1-29

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 01/22408

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 6214842 B1	10-04-2001	NONE	